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Medicine based evidence and personalized care of patients

Ralph I. Horwitz[1] | **Mary E. Charlson**[2] | **Burton H. Singer**[3]

[1]Temple Transformative Medicine Institute, Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA

[2]Weill Department of Medicine, Weill Cornell Medical College, New York, NY, USA

[3]University of Florida, Gainesville, FL, USA

Correspondence
Ralph I. Horwitz, Temple Transformative Medicine Institute, Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA.
Email: Ralph.horwitz@temple.edu

Abstract

Background: For the past 70- years patient care has been dominated by Evidence Based Medicine (EBM) with its emphasis on Randomized Controlled Trials (RCTs) and clinical guidelines to standardize medical decision-making.

Methods: Critical assessment of the literature and analyses of the arguments that favor patient care based primarily on individual variability in disease risk or treatment response versus emphasis on group standardization.

Results: Medicine Based Evidence (MBE) is used to guide decision making for an individual patient at hand by profiling the clinical features (biology) and life experience (biography) of the patient and then finding approximate matches to the patient in a clinical library of patients assembled from diverse sources (RCTs, cohorts, registries, electronic health records and more).

Conclusion: Medicine is transitioning from population based model of clinical care that relies on average results from RCTs to an individual-based model of "personalized" medicine. For individualized care of the patient at hand, MBE is the preferred scientific strategy to generate evidence for patient care.

KEYWORDS

clinical guidelines, evidence based medicine, medicine based evidence, randomized controlled trials

For the past 70 years, evidence generation for patient management in clinical medicine has been dominated by Evidence-Based Medicine (EBM) with its emphasis on Randomized Controlled Trials (RCTs).[1] EBM can tell us about the benefits of treatment in the average patient but not for the patient at hand; for how to initiate treatment but not how to adjust or modify therapy after treatment has started; for treatment efficacy when compared to placebo but less often when compared to other effective treatments; when outcomes are chosen as hard endpoints, but not when the predominant concerns of patients are physical limitations or social functioning or psychological distress.

Over the same time frame, there has been broad acceptance that variation in patient care is bad, and that guidelines must ensure that patients are treated uniformly according to EBM to reduce variation in both the processes and outcomes of medical care.[2] The result of these constraining paradigms is that many clinical decisions in patient care, especially those that require treatment modifications in response to changes over time in disease severity or of comorbidities, are not evidence-based because the evidence that a clinician needs to treat the patient she is seeing now does not exist. How did we arrive at such a situation and what can we do to free ourselves of the current constraints and build an evidence base that better serves the interests of both patients and their physicians in clinical management decisions?

1 | RISE OF EVIDENCE-BASED MEDICINE

For most of the history of medicine, evidence for the effectiveness of clinical therapeutics was based on anecdotal reports and personal experience. Bleeding and purging were accepted treatments because they conformed to accepted but erroneous theory and persisted long after

Pierre Louis used the "numerical method" to demonstrate their ineffectiveness.[3] Lind cured scurvy by feeding citrus to sailors despite having no underlying theory to explain his results and the effect was so dramatic that it achieved widespread adoption.

This approach to evidence generation in medicine changed in 1948 when Austin Bradford Hill adopted R. A. Fisher's method of randomization and reported the results of the first randomized controlled trial.[4] Before then, investigators employed alternate allocation methods (Alternate day or alternate patient) to create similar groups for treatment comparisons. Although these alternate allocation methods were considered an advantage over the previous case method approach, there was continuing worry that selection bias by physicians circumvented the intended similarity by allowing physician preference to decide who received the new treatment. The use of randomization to minimize allocation bias was accompanied by other methods such as placebo controls, double-blinding and "intent-to-treat" analyses that further contributed to the acceptance of the RCT as the best available method for demonstrating the average benefits of treatment in groups of patients.[5]

For large RCTs, the expected similarity of the compared groups at baseline achieved by randomization was reinforced by the principle of "ceteris paribus", all other things being equal.[6] That randomization did not ensure balance on covariates was soon recognized, as the current literature on re-randomization attests the notion of "all other things being equal" is essentially fiction. Forcing balance on a limited list of covariates while simultaneously approximating random allocation is the reality of the world of RCTs. And of course, there was the further reality that postrandomization changes in comorbidity, levels of adherence to treatment and disruptions in social and psychological attributes of patients negates the very idea of ceteris paribus.

Nevertheless, trialists often argue that the results of a well-conducted RCT enable causal inference and permit the conclusion that differences in outcomes are directly attributable to differences in treatment. That argument is dependent as well on the use of statistical methods to eliminate chance as an explanation for the results. If the findings were not due to bias (eliminated in design) or chance (eliminated in analysis) it was argued, and if all other things were equal—or we should say that balance is achieved on a prioritized list of covariates—then it was concluded that a causal explanation for the treatment benefit was all that was left to account for the differences in outcomes.

But the best, most well-constructed clinical trial compares the average effect of one treatment (A) vs a second treatment (B), in which the respective mortality rates might be 23% vs 34% ($P < .01$), clearly indicates that treatment A benefits more of those enrolled in the trial than treatment B. However, for individual patients, the impact is not 23% or 34% mortality—patients either live or die. Similarly, for major health outcomes such as myocardial infarction, stroke, pneumonia and others, the patient either experiences the outcome or does not. Thus at an individual level, the effects of the intervention are either success or failure—there is no average effect.

Rolling up individual outcomes to average effects, which reflects how the treatment worked in the trial population as a whole, actually buries the determinants of individual differences and would relegate everyone to the same "best" treatment, even though it may not lead to the best outcomes in a specific individual.

Clearly, no one would compare the outcomes of treatment in breast cancer patients when those with metastatic disease were randomized along with those with early stage breast cancer. So RCTs are conducted in more narrowly defined groups of patients with more restrictive eligibility to limit prognostic heterogeneity. This sets the stage to ignore treatment heterogeneity and its exploration and individualization of therapy except in clearly important prognostic strata.

The "average" effect as the official result of the RCT has been imbued with a level of veneration that resists challenge. Many trialists and many who promote current methods of EBM decry efforts to explore the determinants of heterogeneity in treatment response as equivalent to blasphemy, to wit, pseudoscience.[7] We argue, however, that this paradigm has retarded scientific progress in addressing issues in chronic illness that are now critical to personalizing medical care. We need to move beyond this outdated reverence for the average effect and focus instead on decision-making for the individual patient.

2 | EMERGENCE OF CLINICAL PRACTICE GUIDELINES

Around 50 years ago, studies of geographic variation suggested that variation in procedures occurred at least in part because of an oversupply of physicians or healthcare institutions leading to unnecessary procedures and contributing to soaring healthcare costs. The dominant view was that variation was bad—including variation that was intended to tailor or personalize clinical care. In support of this view, studies were completed that suggested many treatments and procedures were performed inappropriately and lacked evidence to support their use for individual patient.[8] To address this concern, remedies were sought to reduce variation in the practice of medicine and to promote the average benefit of treatment. The age of promulgation of evidence-based guidelines drawn from RCTs and meta-analyses arrived.

The Institute of Medicine (IOM) defines clinical practice guidelines as "...statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence".[2] In the IOM framework, the summit of the evidence hierarchy is the randomized controlled trial (often requiring meta-analyses to summarize results of many, sometimes conflicting, studies). Observational research studies such as cohort or case-control studies are judged inferior and clinical experience of one or many practitioners is even further diminished in value. In 2011, the IOM noted that there were at least 3700 clinical practice guidelines from 39 countries.[2]

The goal of standardization by guidelines is to reduce variability in the practice of medicine and ensure that all patients with the "same condition" receive the same evidence-based standard of care based on RCTs whenever possible. Much has been made of standardizing treatment for management of diabetes, and we now judge the performance of physicians by control of a patient's haemoglobin A1c, a proxy endpoint that can be assessed over weeks not years. Yet patients treated with insulin to achieve a biochemical endpoint (glucose level) almost inevitably gain weight, adding to the pro-inflammatory visceral fat and cardiovascular risk; and perhaps leading to the finding of increased mortality in the intensively treated patients in the ACCORD study.[9]

Yet, variability in response to treatment and variability in patient outcomes is conditioned on many factors beyond a specific medicine or surgical procedure, including a person's home, family, social and work environment.[10] Variability in clinical medicine results from both individual biology and individual biography (life circumstances and stresses). This paradox has been recognized both in epidemiology and in clinical research.[11,12] We need to move beyond hypothesis testing in artificially constructed experiments to interrogating treatment responses among patients in real clinical practice.

So here is the crux of the matter...and it is the 2 sides of the same coin: individual variability in disease risk and response to treatment in conflict with group standardization in treatment of individuals. Ironically, this debate is occurring at the same time there is a major shift in the specification of evidence to guide clinical practice that has been fostered by recent scientific and technological advances in genetic and molecular science that are unravelling disease pathogenesis at the level of the individual.[11]

At this point, it should be clear that guidelines that purport to optimize patient care cannot, in principle, be derived from RCTs as currently conducted. Without profiling an index case—the patient at hand—you do not know the characteristics of the person for whom you hope to do the optimization. Clinical practice guidelines, because they are developed based on results over heterogeneous *populations*, cannot possibly connect with decision-making tuned to the idiosyncrasies of the patient at hand. The problem of heterogeneity has also been addressed in discussions of the generalizability of trial results. For example, Deaton and Cartwright have argued that if the result of an RCT is, by chance, close to the truth, then the truth being referred to is for the trial sample alone. It cannot be assumed that the result generalizes to other individuals not included or not eligible for the trial.[13]

The mismatch between what clinical practice guidelines offer and what physicians need is easily recognized as the contrast between an atomistic approach to research and a holistic approach to clinical medicine. Guidelines typically focus on a single disease or risk factor studied in many patients, while the clinician cares for a single person with many medical problems. To illustrate the contradiction, consider this example:

> *A 70 year old woman with three chronic diseases and two risk factors, if guidelines were followed, would be prescribed 19 different doses of 12 different medicines at different times of the day. More importantly, there are 10 possibilities for significant drug interactions, either with other medicines or other diseases.*[14]

Few knowledgeable clinicians would choose to follow guidelines that are so potentially harmful to their patient.

3 | ARGUMENT FOR MEDICINE BASED EVIDENCE

Where should physicians look for evidence to guide them when they seek support for management decisions of an individual patient at hand? We have proposed and illustrated a method for individual clinical decisions that starts with the patient for whom a decision in care is contemplated.[5,15] The treating physician produces a comprehensive narrative that profiles the patient and that includes all of the essential clinical elements: biological and clinical, social, behavioural and environmental. The profile is not restricted to a single point in time but rather includes all of the relevant information up to the time of the contemplated decision, for example, whether to start or stop a medication; or whether to add a new one or subtract an old one; whether to modify treatment because of a new comorbidity or worsening of a previous comorbid disease. The clinician then searches a library of patients' profiles to find "approximate matches" who are similar to the patient at hand, some of whom may have received the contemplated treatment, other treatments or no treatment at all. A positive

treatment response among a substantial majority of the approximate match patients who received the contemplated treatment would represent evidence, tuned to clinical practice, that the patient at hand would likely benefit from the contemplated treatment.

We described a method for constructing clinically relevant histories/profiles using data collected but unreported from 2 recent phase 3 RCTs assessing belimumab in subjects with clinically active and serologically positive SLE.[15] In this example, we showed that the richly detailed patient profiles that we developed are sharply at odds with the limited information utilized in conventional EBM and RCT analyses that are the basis for current clinical practice guidelines**.** The role of the constructed profiles is as an initial entry in a library of profiles, each representing the detailed clinical experience of one SLE patient. In contrast to the reported results of the RCT from which the raw data were derived, subsets of the profiles when approximately matched to the profile of a given patient, who need not at all be a case in the original library, now contain the evidence needed to guide decision-making about a treatment option. It is important to emphasize here that the fact that the mini-library we constructed was based on data collected during an RCT is irrelevant. For us, it was a convenience sample. We could just as well have initiated an SLE library using an existing SLE patient registry.

On a much larger scale, and indicative of what is possible with contemporary omics technologies, Chen et al[16] constructed an integrated personal omics profile (iPOP) combining genomic, transcriptomic, proteomic, metabolic and autoantibody profiles for a single patient followed over a 14-month period. Analysis of this biologically rich profile uncovered extensive, dynamic changes in diverse molecular components and biological pathways across healthy and diseased conditions. The use of such profiles in clinical practice would consist of the clinician having available the iPOP information for a patient at hand at several points in time over an unfolding clinical course, at each of which one or more contemplated therapies are considered for administration to the patient. As an evidential guide to the clinician's decision-making, he/she would like to access a library of iPOP profiles and identify those that approximately match the profile of the patient at hand and where some of the matched patients received the contemplated therapy and others did not, essentially acting as controls for comparison purposes. If a substantial majority of the patients identified in the library and receiving the contemplated therapy (ies) had a positive subsequent response, this would serve to encourage use of the therapy (ies) on the patient at hand.

From our perspective, the iPOP profile is only one element of a more elaborate profile characterizing the patient at hand. An array of biomarker assays, demographic, behavioural and social environmental information, and a record of clinical decisions up to any point in the clinical course at which profile library enquiry might be initiated are also to be included in a full profile. Identifying what are to be regarded as approximate matches to a patient at hand might appear, at first glance, to be hopeless given the high dimensionality of an individual profile that includes omits-based information. However, progress on relevant methodology is already available as exemplified by the approximate matching strategies using electronic health records already put forth by Gottlieb et al.[17]

Finally, a few words are in order about what we regard as the importance of behavioural and social environmental information in the patient profile. There is a considerable, and growing, literature supporting links between such information and disease progression. For example, Costanzo et al[18] review a large set of studies focused on cancer progression linked to behavioural factors. Costanzo et al also show that cancer survivors exhibit a resilient ability to respond to day-to-day stressors and challenges. Daily stressors can have a significant impact on survivors mood and physical symptoms and therefore could be an important intervention target. Longitudinal analysis in Costanzo et al suggests improved positive affect, environmental mastery and positive relations with others following cancer diagnosis among cancer survivors.[19] Strategies for promoting these forms of psychological well-being represent another family of intervention targets.

Given the above examples, it is important to emphasize the point that psychological and social environmental evidence are largely absent from data in most current electronic health records, to say nothing about their absence in nearly all RCTs in medicine. Nevertheless, the handwritten narrative portion of patient records of 35+ years ago—and even current ones when the clinician presents a comprehensive summary of a patient at hand—frequently contains nuanced observations about the importance of such factors in patient recovery processes. Although the infrastructure to incorporate narrative information remains insufficient, natural language processing is developing the capability for profiling and approximate matching methodologies. Thus, we emphasize their inclusion in patient profiles going forward and their entry into libraries of profiles that would be used in the approximate matching process described above. Such information, with accompanying ontologies, in a computerized evidential base can enhance clinical judgements and decision-making.

4 | SUMMARY

At the present time, medicine is in the midst of an intellectual crisis as it transitions from a coarse level population-based model of clinical care that relies on "average" results

from randomized controlled trials (RCTs) to an individual-based model of "personalized" medicine. Clinical practice has always focused on the individual patient but Evidence-Based Medicine (EBM) and clinical practice guidelines with their focus on RCTs and populations level inference have failed to provide the evidence needed to manage individual patients.

The challenge today is to enhance the ongoing process of clinical judgement so that the individual clinician and patient can effectively interface with the vast amount of information potentially pertinent to decisions about patient management. We now have the potential for integration of social, psychological and ecological data with basic biological information and prior clinical experience of the physician to put forth profiles of individual patients at an unprecedented level of detail. Medicine based evidence starts with the idiosyncratic detail of an individual patient and, via repeated use of a library containing approximate matches to the given patient provides a stark alternative to population-based clinical practice guidelines and strengthens individual level management of patients in actual clinical practice.

ORCID


Ralph I. Horwitz http://orcid.org/0000-0002-1224-2723

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