

What makes medical knowledge: on the epistemological tensions between “evidence-based medicine” and “personalized medicine”

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Abstract

“Evidence-Based Medicine” (EBM) and “Personalized Medicine” (PM) are both complex, multifaceted movements with significant implications for 21st century medicine’s approach to medical evidence and clinical decision making. Both movements entail a specific vision for an ideal of medicine, as well as recommendations for practices to achieve this ideal. Each movement also implicitly and explicitly involves its own competing set of epistemological assumptions regarding the nature of medical knowledge, which act to inform (and are themselves informed by) these ideals and practices.

These differences in epistemological perspective manifest as multiple tensions between EBM and PM. The movements differ substantially in their approach to the respective roles of theory and evidence in medical knowledge, in some ways echoing the long-standing “empiricism vs rationalism” tensions in Western philosophy. They also differ in their assessments of the nature of medical uncertainty, and of the level of statistical heterogeneity in patient responses. These conceptual differences manifest methodologically as differences in approach to aggregate vs individualized analyses, including subgroup analyses, and in practice as different views regarding individualization and standardization in medical care.

This work engages in an exploration of the history and nature of these movements and explores these conflicts from epistemological and practical perspectives, as well as the potential for a complementary synthesis between the two. While EBM and PM have substantial points of conflict, they share a firm belief in the pragmatic potential for their methods to improve medical care despite the putative limitations of scientific inquiry, and they are not necessarily fundamentally incompatible. The movements must work to actively examine their epistemological assumptions and engage meaningfully with the resulting criticisms in order to define the best path forward for 21st century medicine’s relationship with evidence, knowledge, and decision-making.

Introduction

Diagnostic and treatment decisions are fundamentally concerned with the application of medical knowledge amidst uncertainty. Physicians must engage in numerous daily epistemic inquiries, assessing the quality and value of pieces of theory and evidence in the context of patient specific factors. To whom should a given patient be compared when predicting how they are going to respond to an intervention? How much weight should be given to experience and the idiosyncrasies of clinical context? What sway should be held by the latest clinical trial? What is the role of pathophysiological understanding?

“Evidence-Based Medicine” (EBM) and “Personalized Medicine” (PM) are two movements which seek to engage with such questions and guide physicians in medical practice. They have exerted and will continue to exert significant influence on the approach of 21st century medicine to decision-making. Both movements also implicitly and explicitly entail epistemological assumptions regarding the nature of medicine, knowledge, and medical evidence. Meaningful philosophic inquiry is required to unpack these implicit assumptions, and understand what it is, precisely, that these movements assert.

At surface level the names of both movements hold a deceptive, nearly self-evident simplicity about them. Surely all medical interventions are meant to be based on some form of perceived evidence, and by its very nature medical treatment is always personalized to a degree – the decision of whether to offer a cast or chemotherapy is made with an assessment of the patient’s *personal* presenting complaint. Yet as evidenced by both the bulk of scholarship and the ferocity of debate¹ surrounding both EBM and PM, neither concept is quite so simple. Both EBM and PM are multifaceted and evolving, with numerous perspectives regarding what they do and do not entail. For the purposes of this paper, they are understood to include:

- (i) a vision for an ideal of medical practice
- (ii) a series of recommendations regarding how best to approach this ideal
- (iii) a set of epistemological beliefs regarding the nature of medical knowledge and clinical decision-making

This paper will focus most directly upon the third facet, and the ways in which it both acts to inform and is itself informed by the prior two. This work will outline a brief history of both movements and introduce their relationship to each of the above components. It will further explore the conceptual conflicts between EBM and PM, and the ways in which these are reflected in differences in

practice. Finally, the potential for synthesis between the two will be discussed, including both the improvement of each movement and the prospect of a complementary path forward.

A Brief Introduction to “Evidence-Based Medicine”

As both a concept and a movement, EBM is most prominently associated with the work of Dr. David Sackett and colleagues at McMaster University and Oxford University in the 1980s and 1990s.² It arose as a reaction against medical practices regarded as unscientific, too often rooted in the personal sway of eminent physicians, and excessively focused upon tenuous pathophysiologic rationalizations.^{2,3} Advocates of EBM can point to multiple cases in which “standard” practices have been proven either ineffective or even actively harmful when subjected to rigorous evidence-gathering and study.^{4,5} The dramatic case of prophylactic anti-arrhythmic drugs is particularly insightful: making the evidentially unexamined yet physiologically intuitive decision to prescribe these drugs to myocardial infarction patients likely lead to thousands of unnecessary patient deaths.^{6,7}

The vision of EBM (i) is that of a standardized medical practice strongly driven by objectively determined best evidence practices, with minimal variation from established and validated standards of care.^{2,3} The movement believes this is best achieved (ii) through the deference of clinical judgment to well-constructed syntheses rooted in a clear hierarchy of evidence which places the randomized controlled trial as a gold standard for answering questions about therapeutic effectiveness and through the application of significant skepticism to mechanistic or experiential claims (note that while the n-of-1 trial is considered the ultimate gold standard, it is generally considered practically infeasible to perform).^{2,8} The epistemology of EBM (iii) can be summarized in brief as asserting the fallibility of theory and expertise and believing that the uncertainties surrounding medical care are so substantial as to be irreducible at the level of most individual patients – thus necessitating an aggregated and population-centric approach.⁹

A Brief Introduction to “Personalized Medicine”:

PM is a more recent movement than EBM, with origins traceable to the early 2000s amidst the hopeful promise of the Human Genome Project, and emerging innovations in genomics, bioinformatics, and computational biology.¹⁰ Unlocking the nature of genetic variation was hoped to provide mechanistic insight into the heterogeneity of patient prognoses and responses. Recent developments in artificial intelligence and data science technology have further contributed to the prominence of the movement, as they are envisioned to enable meaningful gathering and analysis of vast amounts of patient-specific information.¹¹ At its core, PM is dissatisfied with EBM’s emphasis upon aggregates in guiding individual treatment decisions – it strives not to answer the question of “will this treatment provide benefit, on average, within this population?”, but rather the question of “will this treatment provide benefit to the specific patient in front of me?” It advocates for the use of patient specific information amidst a mechanistic backdrop to predict and thus personalize at this individual level. PM, too, has scored some prominent victories, such as in the identification and direct targeting of the treatment-relevant HER2/neu breast cancer gene, and the development of increasingly complex tumor prognostic scores.^{12,13}

The vision of PM (i) is that of a personalized medical practice, driven by fluidly contextual best practices through the incorporation of all available information about a given patient’s personal genetic, environmental, and metabolic contexts.^{14,15} Practices emphasized by the movement (ii) include both mechanistically driven -omics techniques, and the use of “Big Data” algorithms to incorporate vast amounts of personal information from sources including hospital monitoring equipment, and personal devices.¹⁵ PM strives to divide patients into smaller and smaller subgroups based upon characteristics deemed to be physiologically or clinically relevant – favoring personalization even at the potential cost of statistical power. The epistemology of PM (iii) can itself be summarized as a belief in the importance of mechanistic physiological theory in contribution to the body of medical evidence, and the conviction that the uncertainties surrounding medical care *are* reducible in meaningful and substantial ways through creative analytical methods.¹⁴

Conflicts between “Evidence-Based Medicine” and “Personalized Medicine”

Conceptual: The Relationship between Theory, Evidence, and Knowledge

EBM and PM differ in their accounts of the nature of medical knowledge in a manner that may be regarded as a continuation of the longstanding battle between “empiricist” and “rationalist” approaches.¹⁶ EBM falls in line with the former school, prioritizing direct observation of the world as the primary source of knowledge, and emphasizing the fallibility of attempting to extend beyond direct evidence.¹⁷ PM shows a greater degree of kinship with the latter, emphasizing the role of a unifying theoretical understanding in integrating medical evidence, and the ability of rational causal analysis to expand upon limited evidentiary pools.¹⁸

EBM acts to reject not only claimed expertise, but all forms of evidence it deems unsystematic. Observational or preclinical studies – as well as mechanistic arguments – may be regarded a potential source of hypotheses but are only likely to be afforded any significant influence upon conclusions or clinical decisions in the absence of evidence from higher hierarchical tiers.¹⁹ Advocates of EBM may justify this conservatism through reference to historical cases in which “rational” medical decisions have proven ineffective. They may fear the return of an “eminence-based” framework wherein particularly persuasive explanations carry value disproportionate to their practical merit and they emphasize the pitfalls of constructing rationalizations atop limited evidence. They advocate instead for a relatively theory-agnostic approach, emphasizing gathering real-world evidence that is directly relevant to practice questions – mainly in the form of large scale, randomized intervention studies.^{3,19}

PM may push back by arguing that EBM is excessively conservative, pointing to cases such as that of the origin of insulin, wherein the theoretical foundations were so substantial that outstanding benefit was realized without any randomized trial being required.²⁰ Further, EBM’s claim toward being a theory-agnostic and solely evidence-driven approach may be called into question on the grounds that all science is theory-laden, and thus the theoretical orientation of those carrying out the trial is reflected in everything from the choice of initial targets, to the choice of

final analyses.²¹ PM acts instead to actively embrace theory, seeking to derive benefit from mechanistic understanding through the adoption of Bayesian and causal approaches.¹⁸ Researchers using such methods attempt to estimate prior probabilities or map networks of mechanistic interconnection between physiological variables and outcomes – with the goal of extending limited observational information and making actionable inferences about unobserved states.

Practical: Aggregate vs Individualized Analyses

One significant practical difference between EBM and PM stems from the latter’s affinity for subgroup analyses of which the former is skeptical.²² The search for subgroups for which interventions may be particularly effective or ineffective is approached by EBM advocates with a significant degree of caution. They warn of multiple comparisons and the danger of spurious results appearing significant due to deliberate or inadvertent “fishing” or “p-hacking” techniques, and of the potential for cyclic synergies between such results and *post hoc* rationalizations.²³ They trend instead toward meta-analyses of ever larger patient groups, seeking surety even at the potential cost of subgroup resolution and individualized mechanistic insights.

Reflecting the rationalist-empiricist debate, that which is perceived as insignificant to EBM’s methods may be regarded as significant to PM in the context of strong Bayesian priors (which may themselves incorporate past theory and observational study). PM stands by these analyses, as they may provide the only means of gaining meaningful insight from data about increasingly narrow groups of patients. They may argue that such analyses are only vulnerable to these criticisms when performed poorly, based upon questionable frameworks, and overstepping the boundaries of gathered data. The case of cholesterol drug dalcetrapib provides a clear example of the potential for subgroup analyses driven by physiological insights.²⁴ While initial RCTs showed no aggregate effect, later pharmacogenomic analysis revealed that this was a result of two opposing subgroups cancelling each other out – that is, while patients with a certain common genetic polymorphism experienced benefit, those with another common genotype were harmed.²⁴

Conceptual: Uncertain and Homogenous vs Certain and Heterogeneous

One of the central challenges of medicine is translating between aggregate knowledge, and the needs of any given individual patient.²⁵ Indeed, it may be contended that scientific methods are fundamentally incapable of truly engaging with the objective reality underlying the situation of an single patient in an uncertain context.^{25,26} Despite this potential line of epistemological criticism, both EBM and PM remain faithful in the ability of their practices to pragmatically optimize patient welfare amidst the uncertainty of the medical world.

Some of the most substantial differences between the movements arise, however, in their beliefs regarding the level at which this uncertainty should be addressed. For example, a “Number Needed to Treat” (NNT) of 10 for a drug to prevent stroke means that, on average, for every 10 patients given the drug, 1 will be exposed to the risk of side effects but have a stroke prevented, while 9 will be exposed to the risk of side effects without

having any event prevented. While EBM aims to establish the NNT and determine whether a new intervention is better or worse than this standard, PM strives to go further and determine whether a given patient is going to fall within the “1” or the “9.”

This difference in approach is informed by important differences in the movements’ assessment of the nature of the uncertainty underlying medical practice. In the context of medicine, there is both informational uncertainty (arising from a lack of acquirable knowledge about the past or present) and intrinsic uncertainty (which cannot be reduced through gathering additional information).²⁷ PM emphasizes the former, believing that many medical questions are practically solvable through the improvement in mechanistic understanding and advances in data gathering and analysis.¹⁵ EBM ascribes a greater magnitude to the latter, emphasizing the depth of complexity in the body – when PM’s holy grail of the human genome failed to answer all medical questions, then came the proteome, the epigenome, the metabolome, and even the exposome to the forefront.¹⁵ EBM advocates believe that only real-world randomized trials can sufficiently grapple with this uncertainty, while PM advocates believe that these other methods can reduce the reducible uncertainty sufficiently to guide clinical decision-making.

The movements also differ in their understanding of the concept of statistical heterogeneity – that is, their assessment of how well measures of central tendency actually reflect any given member of the population.^{28,29} EBM views the response of patients “on average” to be a reasonable predictor of the response of any given patient to the intervention, but PM is wary of this. While EBM is structured to ignore outliers, PM considers them to be crucial both for the mechanistic insights they can offer, and for the sake of providing tailored care to outlier patients.²⁸ While the average of all patient responses may effectively approximate a population response, it is possible that no patient is ever actually an “average patient.” Under an assumption of complete heterogeneity only information about the same patient’s past responses (gained through methods such as n-of-1 trials) might be seen as instructive, while under an assumption of complete homogeneity information about the response of any past patient within the same population would provide perfect information.^{28,30} While neither method places itself at the extreme, their differences in approach to this topic are clearly reflected in their methods.

Practical: Standardization vs Personalization

These epistemological perspectives have substantial consequences upon the visions espoused by EBM and PM for medical practice. In line with its beliefs regarding the homogeneity of responses and the irreducibility of uncertainty at the level of individual patients, EBM advocates for broad standardization in medical practice.³¹ If a patient population is homogenous and cannot be meaningfully subdivided, any given patient must be treated with what the evidence has shown to be best, on average, for that population. This provides a basis for EBM’s embrace of methods such as systematic reviews and meta-analyses to generate clear clinical practice guidelines which provide algorithms for clinical care based on relatively broad patient characteristics.^{2,3,19}

While EBM reflects its origins in the fundamentally population-based field of clinical epidemiology, PM has risen alongside the individualistic movement for person-centred care.³²

Under the assumption of heterogeneity of response, information about the responses of individual patients (or at least deeply and meaningfully divided sub-populations of patients) is paramount. It follows that treatment would be similarly heterogeneous, with variation in practice instead perhaps seen as evidence of healthcare that is adaptable and responsive, rather than a departure from best practice standards. Additionally, whereas EBM places a high premium on the generation of high-quality and specific data, PM's beliefs in the promise of technological advancement and the broad informational reducibility of treatment-associated uncertainties acts to justify the gathering of massive amounts of patient-specific information through multiple modalities.

Toward a Complementary Synthesis

While the aforementioned conceptual and practical conflicts between “Evidence Based Medicine” and “Personalized Medicine” are substantial, the two movements are far from diametrically opposed. Both aspire to achieve the best medical care through careful and accurate appraisal of all available evidence, and both share the belief that, despite contentions regarding the fundamental limitations of scientific methodology, their respective deals for the best medical care can be pragmatically pursued. What they differ in is their conceptual and epistemological approaches to determining what evidence is valuable, and how it should best be used. By understanding and engaging with the epistemological differences and criticisms, each movement may become a better version of itself.

EBM has already begun to adapt itself in response to criticism, making space for increasing consideration of patient values and a broader range of evidentiary sources.³³ The pressures from PM should push EBM further. It must dissociate itself from its false sense of theory-agnosticism and accept that there can be a rationalistic basis for certain subgroups and their analysis.¹⁷ Further, adaptive and personalized clinical trial designs (such as N-of-1 trials and platform trials) should be explored in order to better incorporate within-patient heterogeneity.^{30,31} Finally, the potential contributions of Bayesian approaches informed by carefully validated mechanistic and observational information should be considered, and perhaps be granted stronger standing within the hierarchy of evidence.

Whereas EBM may be characterized as guilty of excessive epistemic humility, PM can be argued to run the risk of epistemic arrogance. The criticisms from EBM must not be taken lightly. It is important to understand the historical context, to be aware of the numerous historical cases in which mechanistic rationality and an excess of faith in emerging methods have combined to lead medicine astray. Caution and rigor must not be discarded amidst the excitement. Even if the intrinsic uncertainty is not nearly so irreducible as EBM assumes it to be, the practical complexity of medical care must be acknowledged and understood. PM methods must engage with EBM methods, and work to prove that their purported benefits at the individual level also bear out for population health.

Given the breadth of medical care, there may be situations in which factors such as the strength of underlying theory, the relative degrees of intrinsic and informational uncertainty, and the level of response heterogeneity favor one set of epistemological perspectives over the other. Utilizing the proper approach in the proper case may enable an approach to medical knowledge that is fluidly contextualized while remaining scientifically and statistically rigorous. Perhaps EBM and PM will be able to achieve a complementary coexistence through concepts which aim to unify the rigor of EBM with PM's embrace of patient variability.³⁵ It may be hoped that methods of pursuing “patient-centred evidence” will result in an “individualized standardization” with “the imposition of standards, regulations, or norms which are tailored to the genes, body condition, culture, social environment, values, needs, and preferences of the individual patient.”^{25,36}

Succeeding in such an endeavor, however, will require both movements to actively engage in epistemological inquiry to understand the assumptions they entail, render explicit the implicit, and work toward meaningful resolution of the conflicts such a process reveals. It will further require an overarching epistemic humility, and the clear awareness that those principles which are pragmatically useful are not necessarily universal absolutes. Such a process would enable EBM and PM both to recognize the value of the other and may even act to better create space for further change when the next, as yet unknown, movement in the world of medical evidence emerges.

Conclusion

“Evidence Based Medicine” and “Personalized Medicine” are both complex, multifaceted, and living movements that are poised to continue to define the course of medicine's approach to evidence and clinical decision-making. Both movements aspire toward a vision for medical practice that is informed by their respective sets of pervasive and powerful epistemological perspectives. The movements differ strongly in their understandings of the relationship between theory and evidence, the statistical homogeneity of medical response, and the nature of medical uncertainty. They are not, however, necessarily fundamentally incompatible, and both hold fast to a fundamental belief that an ideal of medical practice can be pragmatically worked toward despite the limitations of evidence. Engaging with and understanding these epistemic divisions is essential to evaluating the claims of EBM and PM, enabling each movement to improve in response to the criticism of the other, and ensuring medicine finds the right approach to medical evidence and clinical decision-making in the 21st century. While EBM and PM differ substantially as movements, it may yet be possible to strive toward a medicine that is personalized and evidence-based, in line with the ideals of both.

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