

PERSPECTIVE

Evidence-based medicine and precision medicine: complementary approaches to clinical decision-making

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Abstract

Evidence-based medicine is widely promoted for decision-making in health care and is associated with improved patient outcomes. Critics have suggested that evidence-based medicine focuses primarily on groups of patients rather than individuals, but often fail to consider subgroup analyses, N-of-1 trials, and the incorporation of patient values and preferences. Precision medicine has been promoted as an approach to individualize diagnosis and treatment of diseases through genetic, biomarker, phenotypic, and psychosocial characteristics. However, there are often high costs associated with personalized medicine, and high-quality evidence is lacking for effectiveness in many applications. For the potential of personalized medicine to be realized, it must adhere to the principles of evidence-based medicine: (1) evidence in isolation is not sufficient to make clinical decisions—patient's values and preferences as well as resource implications must be considered, and (2) there is a hierarchy of evidence to guide clinical decision-making and studies at lower risk of bias are likely to provide more trustworthy findings.

Key words: evidence-based medicine; precision medicine; decision-making

Evidence-based medicine

Evidence-based medicine (EBM) represents a paradigm for clinical practice that evolved out of a need for greater objectivity in clinical decision-making. EBM is

defined as the “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients,” rather than making clinical decisions solely on clinical experience and

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pathophysiologic rationale.^{1,2} EBM is now widely accepted as optimal practice for decision-making in health care.³

EBM is based on three fundamental principles. First, there is a hierarchy of evidence based on study design—from approaches that are at lower risk of bias (e.g. rigorously conducted randomized controlled trials) to approaches that are at higher risk of bias (e.g. observational studies). Second, informed clinical decision-making requires use of all best available evidence, usually from systematic reviews to avoid selection bias. A notable resource is the Cochrane Collaboration, which provides reviews of evidence from comparative research.⁴ Third, evidence alone is never enough for clinical decision-making, and clinicians must also consider patient's values and preferences.

The application of EBM has been shown to result in better outcomes for patients. For example, the development of the British Thoracic Society's 1990 asthma guidelines led to increased prescription of inhaled steroids and use of personal care plans, and subsequently led to decreased morbidity and mortality rates.⁵⁻⁷ Another example is the UK National Institute for Health and Care Excellence guidelines for prevention of venous thromboembolism following surgery, which led to reductions in thromboembolic complications.⁸

Purported limitations of EBM

Average effects vs. the proportion that benefit

While EBM provides many important benefits to clinical decision-making, it is not without limitations. Some have criticized EBM for focusing on groups of patients rather than on the individual.^{9,10} Specifically, when trialists report evidence for treatment efficacy, the results are often based on the average treatment effect and do not apply to all patients. However, guidance exists for reporting the proportion of patients that experience important benefit, instead of focusing only on average effects.¹¹ For example, high-quality evidence from 27 studies (13 876 patients) supports the notion that opioids versus placebo provide a small improvement in pain for patients with chronic non-cancer pain—an average reduction of 0.64 cm on a 10 cm visual analogue scale for pain.¹² This effect is smaller than the minimally important difference (MID), the smallest change in an instrument score that patients perceive is important, of 1 cm.¹³ If every patient experienced this same effect, opioids should not be used for analgesia in this population; however, the application of methods to calculate the proportion of patients that achieve the MID results in a risk difference of 11%, meaning that 11% more patients with chronic non-cancer pain treated with opioids will achieve important pain relief versus those who received placebo. This translates to a number need to treat (NNT) of nine, meaning that nine patients need to receive treatment to achieve an important benefit in one patient.

Subgroup effects

When pooling results across trials in a meta-analysis, there may be heterogeneity in the treatment effect, which suggests that there may be subgroups of patients (i.e. older, sicker) that have a different response to treatment or vulnerability to adverse effects.¹⁴ EBM has recognized this issue, and provides strategies for exploring possible subgroup effects to guide treatment of individuals with important prognostic factors,^{15,16} however, many reported subgroup effects fail to meet criteria for validity.¹⁷

When credible, clinicians can determine the baseline risk relevant to subgroups of patients, and calculate the expected effect of an intervention by multiplying their baseline risk by the relative risk.¹⁷ For example, consider a patient with a disease that, on average, is associated with a 1% risk of death over the next year, and administration of a certain drug versus placebo has shown a 20% relative risk reduction of death. This equates to an absolute risk reduction (ARR) of 0.2% ($1\% \times 0.2 = 0.2\%$), or a NNT of 500 ($100/0.2 = 500$), meaning 500 patients need to be treated with the drug to prevent one death. Now consider a subgroup of patients (e.g. those with more severe disease burden) who have a risk of death over the next year of 5%—their ARR with treatment would be 1% ($5\% \times 0.2 = 1\%$). This translates to a NNT of 100 ($100/1.0 = 100$), meaning 100 patients need to be treated with the drug to prevent one death.

N-of-1 trials

Randomized controlled trials (RCTs) are the most methodologically rigorous study design to establish evidence of treatment efficacy; however, the results are only generalizable to patients that resemble the study population. To maintain methodological safeguards against risk of bias in RCTs (such as random sequence generation, allocation concealment, and blinding) and to ensure applicability to individual patients, N-of-1 RCTs have been proposed for evaluating treatment effects in individuals.^{18,19} In such trials, the experimental intervention and control (or a competing therapy) are administered in pairs and ordered randomly to confirm the effectiveness of treatment among individual patients.¹⁸ Treatments are separated by a washout period, a designated period of time when a participant is taken off a study intervention to eliminate the effects of the treatment. The number of pairs of interventions typically varies from two to seven, but the clinician and patient can decide to stop when they establish that there are, or are not, important differences between interventions (Fig. 1).

Precision medicine

Precision medicine (PM), otherwise known as personalized or individualized medicine, tailors the diagnosis and treatment of diseases to the individual based on genetic, biomarker, phenotypic, or psychosocial

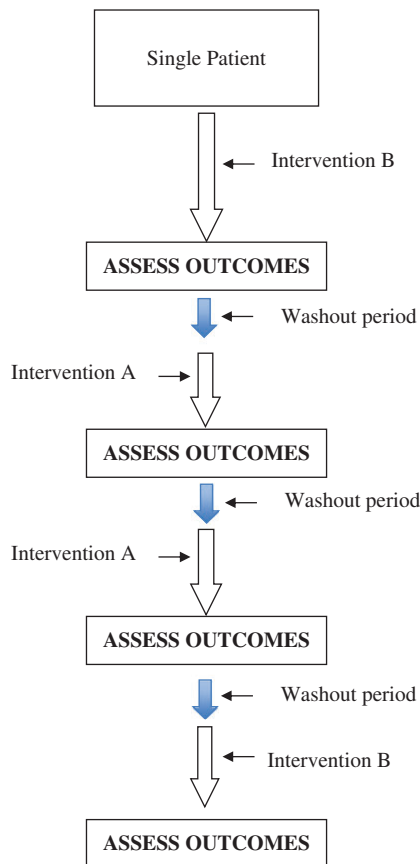


Figure 1. Basic design for N-of-1 randomized controlled trial.

characteristics; in other words, it is the concept of administering the right treatment, to the right patient, at the right time.²⁰ The recent completion of the Human Genome Project, along with technological advances for characterizing patients using proteomics, metabolomics, and genomics, provides a unique and exciting opportunity for PM to play an important role in clinical decision-making.²¹ Proponents of PM suggest it has the potential to re-focus medicine from reaction to prevention, direct the selection of optimal therapy, improve quality of life, reduce adverse drug reactions, increase treatment adherence, and reduce overall health care expenses.^{22,23}

Shift from reaction to prevention

The field of oncology holds great promise for the application of PM as a result of increased understanding of oncogenic mechanisms.²¹ For example, women with certain BRCA1 and BRCA2 gene mutations have a 72% and 69% risk of developing breast cancer, and a 44% and 17% risk of developing ovarian cancer, respectively.²⁴ Furthermore, the molecular diagnosis of germ-lines rearranged during transfection mutations in individuals with multiple endocrine neoplasia type 2 allows for codon-directed prophylactic thyroidectomy and regular

screening for pheochromocytoma, medullary thyroid cancer, and hyperparathyroidism.²⁵ These advancements in technology enable clinicians to identify at-risk individuals with genetic tests, and promote preventive measures, such as increased frequency of imaging, chemoprevention, and prophylactic surgery.²²

Direct the selection of optimal therapy

Up to 50% of patients do not respond to initial treatment for diseases such as arthritis, diabetes, asthma, or depression.²⁶ It has been suggested that, in some cases, differences in response to treatment are related to mutations in genes that code for drug-metabolizing enzymes, drug targets, or drug transporters.²⁷⁻²⁹ For example, diagnostic tests are commonly used to determine which breast tumors over-express the human epidermal growth factor receptor type 2 (HER2), a biomarker that is associated with worse prognosis but also predicts a better response to trastuzumab—a monoclonal antibody.³⁰ Moreover, an estimated 40% of patients with metastatic colon cancer do not respond to cetuximab and panitumumab because of mutations of the KRAS gene.³¹ This discovery led to recommendations that only patients without mutations of the KRAS gene should be treated with cetuximab and panitumumab.³²

Reduce adverse drug reactions and increase adherence to treatment

It has been estimated that up to 5.3% of all hospital admissions are related to adverse drug reactions.³³ Many adverse drug reactions result from variations in genes that code for drug-metabolizing enzymes, such as cytochrome P450 (CYP450), which can result in drugs being metabolized either slower or faster than normal.^{34,35} As a result, some patients may have difficulty eliminating certain drugs, leading to potential overdose toxicity, while others may eliminate drugs before they are able to have an effect. For example, 5-8% of HIV patients managed with abacavir may experience multi-organ system hypersensitivity because of presence of the HLA-B*5701 gene.²² This adverse reaction can be fatal in some cases, which has now prompted genetic testing for almost all HIV patients receiving abacavir. Reducing potential adverse drug reactions through genetic testing is one way to improve patient adherence to treatment. Another way to improve adherence is through knowledge of genetic predisposition to a condition. For example, patients who screen positive for predisposition to familial hypercholesterolemia, and are made aware of this, have a treatment adherence to lipid-lowering medication of 86% after 2 years, compared with 38% prior to testing.³⁶

Limitations of PM

Limited evidence of clinical benefit

Although the promise of PM is enticing, and broad implementation of multiplex hotspot testing is feasible, only 13-40% of patients enrolled into genotype-matched

trials have presented with actionable alterations, which risks attenuation of treatment effects.^{37–40} With this in mind, the current evidence suggests that clinical benefits of biomarker-based treatment strategies may be limited.^{41,42} For example, a 2016 systematic review of 346 studies that compared phase 1 cancer drug trials with biomarker-based treatment strategies to trials without this approach concluded that a personalized approach resulted in a median progression-free survival of 5.7 months (95% CI 2.6–13.8) versus 2.95 months (95% CI 2.3–3.7).⁴¹ This review, however, did not assess risk of bias of individuals trials, or the overall quality of evidence for the outcomes they reported on, and was unable to assess effects on overall survival because of insufficient data.

Limitations of biomarkers and molecular targeted drugs

The diagnostic accuracy of genetic tests is limited, and not all genetic markers have clinical significance. For example, there are reported cases in which women have undergone unnecessary removal of their ovaries after receiving false positive results of genetic testing.²⁰ There is a great need for better biomarkers to assist with the diagnosis of diseases to help guide optimal treatment. Furthermore, even if accurate genetic tests are established, molecular targeted drugs must be developed that are able to successfully target signaling pathways. Available molecular targeted drugs only partially inhibit signaling pathways and may be too toxic to be used in combination. In addition, although some drugs can target signaling pathways in cancer patients, cancer cells have the capacity to develop a resistance to them by up-regulating the pathway or activation of alternative pathways.^{43,44}

Although the above examples largely focus on genetic information to guide PM, this approach also makes use of differences in patient's biomarkers, environment, and lifestyle to customize care. Preventive or therapeutic interventions can then be offered to those who are most likely to benefit, sparing expense and side effects for those who will not.

Policy challenges and costs

There are policy challenges to the widespread uptake of PM, such as the regulation of genetic tests in such a way that encourages innovation but also protects patient confidentiality.^{20,45} Health and drug regulatory authorities need to establish clear guidelines for the identification and approval of personalized drugs and their related diagnostic tests for clinical use.^{20,22} Furthermore, the costs of developing and marketing new molecular targeted drugs are high, and may divert resources from the development of more clinically effective drugs. If health and regulatory authorities are to fund PM research, there should be independent assessors who regularly appraise the cost-benefit ratio

of targeted drugs.⁴⁶ Until there are more studies demonstrating clinical effectiveness of molecular targeted drugs, it may be difficult to justify their high costs.

Conclusions

While EBM and PM have their own merits and limitations, these approaches complement rather than oppose one another. The promise of personalized patient care is powerful and has the potential to fundamentally change health care; however, more high-quality evidence is needed to guide the application of PM to areas in which the benefits outweigh the harms.

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