EVIDENCE-GENERATING RESEARCH AND EVIDENCE-BASED MEDICINE

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Evidence-Based Medicine acknowledges Evidence-Generating Research that informs clinical practice but does not wholly determine patient decisions. As it matures, it will be widely applied, and with further development it may become a complete Theory of Medical Choice. Experience with Evidence-Based Medicine can inform the broader pursuit of an Evidence-Influenced Society.

PHILOSOPHICAL AND HISTORICAL BACKGROUNDS

Four or more millennia ago, and in a few cities across Asia and in ancient Egypt, professionals emerged to care for patients. With little distinction between medical, popular and folk remedies, the therapeutic relationship was central and services were allocated under scarcity (i.e. by price). Knowledge accumulated slowly by observation, but there was no systematic experimentation because practitioners had little basic science and no formal research strategy or methods. Training was by apprenticeship, passing on received knowledge that had been tested by time (e.g. surgery, standards of care). This successful enterprise of *Tradition-Based Medicine (TBM)* persists today for providing many medical, complementary and alternative therapies.

Similarly, the history of *Evidence-Based Medicine (EBM)* started in biblical times (Daniel 1 and First Samuel 5-6), and progressed within Greek, medieval Europe and Islamic medicines (Cumston, 1987). However, Aristotelian Scholasticism (c.1100-1500) reinforced TBM in universities and medical schools by giving overwhelming presumptive authority to forebears, with reasoning by deduction and using experience only for illustration. Aristotelian Scholasticism was overturned in the Enlightenment, from Bacon to Locke, as scientific methods and inductive reasoning were promoted to create new knowledge, to improve human well-being, and to reduce suffering. Royal Societies decisively shifted the emphasis onto empiricism and quantification, the "new philosophy" (Heilbron 2003). Thereafter, nosology, epidemiology, public health laws and medical training in hospitals emerged (Lawrence, 2003; Wilson, 2003). Then (c.1800-1970) the following appeared: far more statistical methods; medical professionalism, schools, journals and law; pharmaceutical businesses; clinical epidemiology (CE); public organizations for research and fund-raising; welfare states and the beginnings of Health Economics (Carleton 1977 and Jones 1996). At McMaster University in the 1970's, CE was re-invented as EBM through consolidation of principles and by structuring methods, as summarized in a series of articles in *Can Med Assoc J*, in 1983. The focus was to reform TBM one doctor at a time through critical appraisal of literature ("evidence") and by evaluating personal experience. This combination was deemed a "basic clinical skill" and was recommended for teaching residents (EBMWG 1992). Later, guidelines, guideline organizations, and EBM journals and textbooks appeared and EBM began to affect government policies, regulations and public financing of care. Therefore, by 2010 EBM affected daily practice (prevention, treatment, survivorship and palliation) in oncology and cardiology -- reflecting for these diseases high incidence in developed countries (and so large sample sizes, drug-oriented research), measurable outcomes, and preventive and adjuvant options.

LIMITED AND EXPANSIVE DEFINITIONS OF EBM

EBM has been controversial (see e.g. Cohen et al., 2004). The main reason for this is that many people have not distinguished between a patient and a Case. The Case is a standardizing abstraction of a patient's predicament. Each type of Case is delineated by a small set of characteristics, and patients who share identical Cases form a cohort that can be assembled for research (Lawrence 2003). *Evidence-Generating Research (EGR)* then yields claims about how best to prevent or manage Case-cohorts. In EGR, heterogeneity of decisions constitutes "protocol violations." In contrast, within EBM the process of informed consent usually includes acknowledgement by clinicians and patients of the relevant Case and any related EGR. However, patient particularities are accommodated with freedom to customize decisions and treatments. In EBM, heterogeneity can be "good clinical judgment" or "patient autonomy." Failing to distinguish

In C. Reading (Ed.), *Data and context in statistics education: Towards an evidence-based society. Proceedings of the Eighth International Conference on Teaching Statistics (ICOTS8, July, 2010), Ljubljana, Slovenia*. Voorburg, The Netherlands: International Statistical Institute. www.stat.auckland.ac.nz/~iase/publications.php

patient from Case, individuals and organizations want current best evidence to wholly determine clinical action. For them, EBM is defined as "the conscientious explicit…use of current best evidence in making decisions about the care of individual patients" (Sackett et al. ,1996), where *use of* is taken to mean *adherence to*. This is a normative application of EGR and may be called *Case-Based Medicine (CBM)*, where deviation is misbehavior or "malpractice." This strong position of CBM is held against a TBM that is taken in caricature form as mere "opinion." This reduced TBM is viewed as the comedic, tragic or farcical foil to the virtues of CBM. Notably, and inappropriately, experience and expertise are set as the lowest possible quality of evidence (DeVoto et al., 2006), and are given no independent status outside EGR. Consequently, venerable Clinical and Academic Review articles that capture clinical observation and nuance are no longer published in many journals -- there is deference to reports of randomized trials, meta-analyses, and guidelines. Lastly, scientific administrators (e.g. political "Progressives" and health-reform advocates) along with some promoters of guidelines believe that their expertise and central, privileged locations in organizations or government uniquely qualify them to make decisions of policies and budgets to direct behavior (Broom, 2009; Sowell ,2009).

In contrast, EBM has been defended as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients…integrating individual clinical expertise with the best external clinical evidence from systematic research…[E]vidence can inform, but never replace expertise,….[which] is reflected … especially [in the] compassionate use of patients' predicaments, rights, and preferences…[and] this may raise rather than lower cost" (Sackett et al., 1996). This acknowledges humanity, standards of care, entitlement and law. It justifies review articles that craft and shape clinical judgment, help to identify and prioritize research questions, and reflect Clinical Scholarship (RCPSC, 2001).

FRAMEWORKS AND CONTENTS OF EGR AND EBM

Specific EGR studies occur within a large frame of options. First, there are two main types of research questions. Baseline classification (e.g. diagnosis) is studied by attending to sensitivity and specificity, Receiver-Operating Curves, predictive values, and likelihood ratios. Exposure studies address etiology, treatment and prognosis, building on classification (used to get the Case-cohorts for study) but add measures for exposures and effects. These concern causes, like age or treatment proficiency, and effects, like survival or quality of life. Second, two hierarchies are superimposed on the two research questions to stratify studies by quality (low to high, or levels of evidence elaborating on Feinstein, 1985) and cost considerations (whether costs are excluded or included, as with economic analyses per Drummond et al., 1987). For example, diagnostic tests are developed and then are compared in a randomized trial to decide whether combining tests gives better patient outcomes. Similarly, Case-series can suggest risk-reduction or therapeutic benefits to be confirmed in a randomized trial. The two hierarchies are complex and controversies about the general ordering are not resolved. For example, is a meta-analysis of randomized trials a superior level of evidence as compared with a large randomized trial? Do other grounds for willingness-to-pay (e.g. psychology, duty) provide more insight than neo-classical welfare economic theory (Jones, 1996)? On balance, these hierarchies are essentially correct, but the in-house debates (e.g. amongst health economists) require further research (i.e. methodology). In summary, central principles of EGR are: quantification (i.e. measurement, statistics); surrogacy (measurement stands in for preference); linearity (cause-to-effect); hierarchy (by design, sample size, methods and economics); and summation (meta-analyses).

The primary goals of EGR are to change belief (i.e. affirm or reject hypotheses) and to change recommendations for a Case-cohort. A research question identifies the target Case-cohort, the contrasting options being tested, and the outcome for the main statistical test. In the corresponding protocol, the general EGR framework is "collapsed" to become a specific study that will collect the minimum data required to answer the research question. Each protocol decision is explicitly justified (e.g. about study design, measurement and analysis). Those decisions respond to ethical, resource and other constraints that make it impossible to conduct a single, comprehensive study with optimal design, large sample size, multiple measures, cost and impact assessments, and participating subjects determining what is clinically significant from their experience. Feasible, efficient research provides sufficient and not exhaustive evidence. The ethical principle of justice

requires that just enough resources be spent on one study so that other studies can be funded (e.g. for other Case-cohorts) or resources are left for other purposes.

Of course, EGR studies are often done as a pattern of research. A pattern may demonstrate steady increase in study quality and move from pre-clinical to post-marketing questions. A pattern slows progress and uses more resources but assures patient safety and regulatory oversight. It uses randomized clinical trials to definitively test likely hypotheses. In addition, a study cannot generate all relevant knowledge claims. For example, an administrator wants cost-effectiveness data, a pharmacist wants pharmacokinetic data, and a clinician wants survival and quality of life data. Patient burden and study resources limit what can be collected, so several studies are required. Even so, modeling and assumptions may then fill in gaps to advance decision-making.

Findings from EGR are acknowledged in EBM in the following manner. Clinical consent is an *ex ante* construction of a *preference* for future *experiences* under *uncertainty* regarding what will actually transpire (Jones, 1996). Therefore, one clinical task is to help a patient access and accommodate evidence from research, to the extent that the patient wants it, to help a patient engage the clinical question and construct a preference that leads to action. Best empirical findings and knowledge claims from a single Case or Case-cohort may help a patient who has that Case anticipate future personal experiences, contingent on choice and probabilities (uncertainty). However, the patient cannot be reduced to the Case. My experience with patients, where EGR findings are applicable, is that only one-half to two-thirds adhere to EGR-recommendations. Patients do reject EGR-based recommendations and fail to follow guidelines. First, there are extra considerations: values for the variables (e.g. use of complementary therapies); patient values (e.g. risk attitudes, time-discounting, inconvenience); patient-centered meanings and interpretations (e.g. of care, of imputed causal sequences); and chosen decision strategies (e.g. heuristics, satisficing). Second, there are tacit, mundane and other types of knowledge (e.g. emotions). Third, the clinical context has many professional, ethical, legal and other constraints. For example, patients cannot be compelled to take a treatment, but are free to omit it. Professionals in their acts of commission must pursue a positive therapeutic ratio, taking into account the whole patient about whom relevant aspects (e.g. values, co-morbidities) were not studied by EGR.

FURTHER CLARIFICATION AND EVOLUTION OF EGR AND EBM

For EGR, researchers need to clarify its limits. Many clinical studies cannot be conducted due to opportunity cost (i.e. limited research funds), ethics, poor measurement tools or very small sample sizes. EGR is most applicable to new pharmaceutical agents where research is well-remunerated and it is mandatory for regulatory approval. Given that pattern of research funding, absence of evidence about something is common but it is not evidence of the absence of something, or its level of clinical relevance. For example, there is scant research into patient well-being and little research on preference. Sample size is becoming a greater challenge as sub-groups of Cases are defined. This will worsen with “personalized” gene- and epigenetic-medicine. There is also little evidence about how to extrapolate from studies with fit patients and only one disease to unfit patients with many diseases (Hampton, 2002). Computer models (e.g. the cell) will emerge, but recommendations from models will need an assigned level of evidence.

For EBM, clinicians need to clarify its limits. Many clinicians cannot keep up with the industry of EGR and guidelines, because the time-cycle of knowledge creation is short in contrast to the longer time-cycles of personal critical appraisal and assembling clinical consensus and wisdom. Clinicians who rely on evidence cannot validate much of it, even if they are able to expertly read, appraise, interpret and accommodate the literature. Clinicians are therefore placing ever more trust in those who direct, fund and conduct EGR. How much of a responsibility is there for a clinician to discuss Case-related evidence with a patient? If there is no limit then the “informed” part of informed consent can take a lot of clinician time. When a patient is a citizen in a political market for care and the budget restricts patient options, must options that are not funded be discussed? Even in the U.S. by 2011 a majority of health-care costs will be paid for by government as entitlements. Therefore, the overwhelming authority of patient autonomy will come under increasing challenge.

THEORIES OF MEDICAL CHOICE

This brings us to the project of constructing a theory of choice for medical services (Jones 1997a & 1997b). A *Theory of Medical Choice (TOMC)* is a system of assumptions, accepted principles and rules of procedure, developed to analyze, help explain, and guide the decision-making process and its resulting allocations of resources for medical goods and services. There are several candidates for a TOMC: TBM; a normative EGR (i.e. CBM); and EBM as either *Scientific Medicine* practiced in a free-market context (as in the United States) or *Scientific Medicare* practiced with public funding (as in Canada, see Jones, 1997b). The question arises as to whether any of these candidates constitutes a sufficiently powerful, insightful TOMC. First, TBM is complex in practice and it is poorly articulated. For today's civil societies, TBM has insufficient lines of accountability and insufficient links to EGR to justify public funding, while patients in a private market might want to know about findings from EGR when making decisions. Second, CBM is not a realistic TOMC because it excessively undermines expertise, patient autonomy and whole-person care. Last, EBM is clearly greater than TBM and CBM, because both of those are defaults within EBM. That is, CBM is applicable when a patient wants to let evidence about the Case determine the decision, and TBM is applicable to many patient predicaments where there is but scant or poorer evidence. Regardless, EBM as Scientific Medicine or Medicare, and with those defaults of TBM and CBM, is not a complete TOMC. To overcome this shortfall, EBM must be expanded in at least two directions. EBM has to direct research into providing a technological toolkit for the clinical context that can rival and balance the kit exploited in EGR. This research program will explore patient decision-making (e.g. roles of affect and values) (Jones, 1994; Montori, 2008) and provide methods for patients to optimize personal methods, strategies, and time spent with clinicians (Barratt, 2008). It can give greater scope and power to philosophy and the humanities as ways of understanding and establishing meaning. Also, EBM has to incorporate principles that give real scope and power to the social sciences beyond Health Economics. This would include hysteresis of decisions, and how decisions are shared by a community of stakeholders with differing motives, economies and flexibilities. Transformative extensions to EBM can shift the focus away from the present over-emphasis on technical and economic efficiencies and towards a better integration of EGR technology with individual and collective human values and aspirations (Jone,s 1994b).

Only time will tell whether EBM can become a complete TOMC, one that balances or harmonizes disparate parts that have to be brought together for an acceptable sharing of practices, budgets, and patient consent. Meanwhile, we may seek a simpler version of the greater vision by agreeing upon a method for decision-making that stands in for a complete TOMC (Jones, 1994b). For example, systematic summaries include posted guidelines (see the National Comprehensive Cancer Network website) but Clinical Practice Guidelines were conceived (at McMaster University) and adopted (by Cancer Care Ontario) as a conceptual 'loop' that might incorporate an indeterminate set of institutional, economic and political factors to determine public funding (Browman et al., 1995), or what is privately insured. The loop was highly schematic and it has not been further developed. Even so, everyone today could support developing a more complete TOMC for the long term, yet identify and share assumptions, rules of evidence and processes of decision-making, for short term practical use. Stakeholders can then allocate resources by transparent, accepted methods. This might work well for certain types of decisions, such as adjuvant therapies in cancer.

IMPLICATIONS FOR TEACHING

In the clinic, patient education is increasingly transmitting the approach of EBM and Case-related research findings, in order to promote decision-making and to satisfy informed consent for action. But this is done one patient at a time by front-line staff, and serious consideration should be given to less expensive methods, applied prior to patients making major decisions (Barratt, 2008). Public education is also required, so that the public can support EGR, medical practice, and government policies, and so participate meaningfully and effectively in health-care reform.

The training, professional development and continual learning of researchers and clinicians must be revised. Regarding EGR, learning and skill-development needs to be balanced and should include: (1) the two types of questions; (2) the hierarchy of evidence, according to design and rules

of evidence (e.g. strength of association, statistical strategies, and methods), and the hierarchy of economic analyses and theories (e.g. Choice, Social Choice, Rationality and Subjective Value); (3) what constitutes a good research question, protocol, study implementation, and analysis; (4) how, for a pattern of research, the EGR framework is collapsed into multiple protocols as separate studies, each with limited and differing sets of quantitative measures and test statistics, but which collectively stand in as decisive surrogates for a single, comprehensive study; (5) how trials, systematic reviews and guidelines result in Case-Cohort recommendations; and (6) how EGR findings become a component in EBM. Regarding EBM, clinicians need sufficient learning in EGR to apply it to clinical practice. Basics must be taught in initial training (e.g. in nursing, physiotherapy, pharmacy and medical schools) but EGR-technologies are maturing so continuing education must include updates and skills training. Clinicians who transition to investigators, decision-makers within organizations or governments, and advocates for health-care, must acquire additional knowledge and expertise in EGR and about civil society.

SUMMARY

EBM appropriates evidence from research to help people make personal decisions about risk-management, tests, treatments and follow-up options. EBM represents a series of philosophical and technological advances that collectively help improve well-being and reduce suffering. Greater application of EGR inside EBM will help rationalize medical recommendations and policy decisions. However, the "Based" in EBM was really a poor choice of a word because the evidence is restricted to knowledge claims based on research and such evidence typically plays only an "influencing" role, or is simply "acknowledged," in a decision-making. A critical distinction for both clinical care and population actions (screening and risk-oriented interventions) is to recognize that EGR generates recommendations about how to manage Case-Cohorts. Both patients and citizens are more than their respective Cases. Personal autonomy is an accepted ethical principle when making health-related decisions in both of these contexts, regardless of recommendations arising from EGR. Neither EGR nor EBM constitute a full-throttled TOMC. That we do not yet have a complete, working TOMC is not a bad thing (Jones 1994b). Competing strategies strengthen, accelerate, evolve and shape one another. In the meantime there is greater space for Patient-Based Medicine, wherein patients have more options and can exercise greater personal freedom. Finally, research needs to better address clinical practice, patient decision-making, organizations and social sciences, in order to deepen and expand EBM towards a TOMC.

IMPLICATIONS FOR NON-MEDICAL DECISION-MAKING

Experience with EBM is relevant to pursuing an Evidence-Based Society. Unexpectedly perhaps, EBM is *not* a good model for other disciplines. EBM is not yet mature so its full implications are unknown. Second, teaching and implementing EBM are presently centered on EGR and critical appraisal, and target technical and economic efficiencies. These themes may not be at issue for many non-medical decisions. Third, obtaining patient preferences for a limited number of personal decisions is difficult but routine, while obtaining and using social preferences to guide collective decisions that affect many people is problematic, rare and very restricted (e.g. elections). There are simply too many societal decisions to make, while substantial expertise is needed to make some societal decisions. Fourth, citizens have weaker rights and far less control over non-medical societal decisions, as compared with the much stronger patient rights and control over clinical decisions. Despite limitations in applying an evidence-based strategy outside of medicine, EBM casts a profound vision for non-medical decision-making by assigning real weight to ethics and personal responsibility, and understanding how decisions and policies can affect a person in many ways. Businesses, organizations and governments could certainly exercise more due diligence in such aspects when making decisions for, or with, consumers, clients and citizens.

In contrast to EBM, EGR *may* be a good model for, or approach to, *some* non-medical societal decisions. However, contemporary debates illustrate obvious limits to the influence of evidence in decision-making. Examples include: (1) whether climate change should be managed; (2) whether a Progressive administration gives superior citizen outcomes to constitutionally limited government; and (3) whether criminals are given appropriate punishment and enough opportunity to self-reform and reconcile with victims and families. Despite research lying around, many

situations are subject to strong ideologies, passions, operating precedents and constraints (paths chosen, and organizational, legislative, legal, and regulatory boundaries). Moreover, debates are typically simplified, along with early satisficing in a search for answers. It remains to be seen to what extent evidence can influence or determine societal decisions, how willing people are to give some or all decision-making authority to experts and evidence, and how we can best get public involvement and apply social preferences to decision-making.

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