MEDICINE'S EPISTEMOLOGY: MAPPING THE HAPHAZARD DIFFUSION OF KNOWLEDGE IN THE BIOMEDICAL COMMUNITY

Lars Noah*

The state of med[i]cine is worse than that of total ignorance. Could we divest ourselves of every thing we suppose we know in it, we should start from a higher ground [and] with fairer prospects.

Thomas Jefferson[1]

I presume nobody will question the existence of a widespread popular delusion that every doctor is a man of science.... As a matter of fact, the rank and file of doctors are no more scientific than their tailors.

George Bernard Shaw[2]

I. INTRODUCTION

By some accounts, we have transitioned to a "knowledge-based" economy dominated by providers and users of various information technologies.[3] Undoubtedly, some sectors of today's economy deserve such a label and perhaps

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* Professor of Law, University of Florida; J.D., Harvard University (1990); B.A., Harvard University (1986). I presented earlier versions of this paper to the faculties at the Georgetown University Law Center (as part of the Sloan Interdisciplinary Workshop series) and at the College of William & Mary School of Law.

1. THOMAS JEFFERSON: WRITINGS 1065 (Merrill D. Peterson ed., 1984) (letter to William Green Munford, June 18, 1799); *see also* RICHARD HARRIS, A SACRED TRUST 5 (1966) (quoting one researcher's estimate that 1912 was "the first time in human history [that] a random patient with a random disease consulting a doctor chosen at random stood better than a 50-50 chance of benefiting from the encounter").

2. GEORGE BERNARD SHAW, THE DOCTOR'S DILEMMA: A TRAGEDY xxiv-v (1906).

3. *See* DANIEL BELL, THE COMING OF THE POST-INDUSTRIAL SOCIETY 14 (1973); PETER F. DRUCKER, POST-CAPITALIST SOCIETY 45–47 (1993).

have always done so. By definition, many professional services are knowledge-based, and professionals define themselves as—and derive their claim to authority from—having specialized expertise.[4] This is certainly true of the medical profession.[5] In fact, the word "doctor" comes from the Latin term *docere*, which means "to teach."[6] If specialized knowledge represents a fundamental feature of the health professions, then why does "evidence-based medicine,"[7] a term coined just one decade ago to describe an approach that its leaders have proclaimed to represent a "paradigm shift" in medical practice,[8] seem like such a novel concept?

As Michel Foucault explained, members of epistemic communities develop "discourses," and he used the medical profession as an illustration of one such discursive community.[9] Noting the doctor's "role as an intermediary in the diffusion of medical knowledge,"[10] Foucault observed that clinical medicine did

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4. *See* ANDREW ABBOTT, THE SYSTEM OF PROFESSIONS: AN ESSAY ON THE DIVISION OF EXPERT LABOR 52–57 (1988); SAMUEL HABER, THE QUEST FOR AUTHORITY AND HONOR IN THE AMERICAN PROFESSIONS, 1750–1900, at 5–8, 354 (1991).

5. *See* ELIOT FREIDSON, PROFESSION OF MEDICINE: A STUDY OF THE SOCIOLOGY OF APPLIED KNOWLEDGE 337 (1970); PAUL STARR, THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE 4, 18–19, 142 (1982); Eric J. Cassell, *The Changing Concept of the Ideal Physician*, 115 DAEDALUS 185, 186–88, 193–94 (1986); David M. Mirvis, *Physicians' Autonomy–The Relation Between Public and Professional Expectations*, 328 NEW ENG. J. MED. 1346, 1347 (1993) (referring to the profession's "monopoly over information"); *see also* Mark A. Hall, *Institutional Control of Physician Behavior: Legal Barriers to Health Care Cost Containment*, 137 U. PA. L. REV. 431, 477–78 (1988) ("Physicians trumpet the scientific basis of medicine when it suits their purpose. At the turn of the century, the medical profession relied on the scientific foundation of allopathic theory to establish exclusive authority over the domain of medical practice through licensing legislation."); *id.* at 478 (adding that the medical profession "plays both sides of the science/art fence in order to maintain complete freedom from control").

6. *See* III OXFORD ENGLISH DICTIONARY 570 (2d ed. 1989).

7. *See infra* notes 35–41 and accompanying text.

8. *See* Evidence-Based Medicine Working Group, *Evidence-Based Medicine: A New Approach to Teaching the Practice of Medicine*, 268 JAMA 2420, 2420–21 (1992); *see also id.* at 2421 ("The underlying belief is that physicians can gain the skills to make independent assessments of evidence and thus evaluate the credibility of opinions offered by experts."); Gordon H. Guyatt & Drummond Rennie, Editorial, *Users' Guides to the Medical Literature*, 270 JAMA 2096, 2096 (1993) ("Without a way of critically evaluating the information they receive, clinicians are relatively helpless in deciding what new information to incorporate into their practice. They may choose to believe the most authoritative expert or the trusted colleague, but they have difficulty exercising independent judgment."). *See generally* THOMAS S. KUHN, THE STRUCTURE OF SCIENTIFIC REVOLUTIONS (3d ed. 1996) (describing paradigm shifts triggered by growing discontinuities between theories and evidence).

9. *See* MICHEL FOUCAULT, THE ARCHAEOLOGY OF KNOWLEDGE 48–49, 182–83 (A.M. Sheridan Smith trans. 1972).

10. *Id.* at 53; *see also id.* at 52 (summarizing "the positions that the [doctor] can occupy in the information networks (in theoretical teaching or in hospital training; in the system of oral communication or of written document; as emitter and receiver of observations, case-histories, statistical data, general theoretical propositions, projects, and decisions)").

not qualify as a science in post-Revolutionary France in part "because it involve[d] a scarcely organized mass of empirical observations, uncontrolled experiments and results, therapeutic prescriptions, and institutional regulations."[11] He described the production and diffusion of biomedical knowledge in the late eighteenth century as reflecting the emergence of a "collective consciousness."[12] Although the proponents of evidence-based medicine trace its origins back to Paris around this same time period,[13] and important parallels persist two centuries later, the discursive community in medicine today faces radically different challenges.

In the practice of medicine, uncertainty is both inevitable and disquieting.[14] At least two things account for this endemic uncertainty: "first, defects in the knowledge of the individual physician and, second, the inadequacies of the profession's knowledge."[15] As another commentator explained, "only a small percentage of medical therapies have been scientifically proven, and even definitive research supporting or refuting particular therapies is often misunderstood and misapplied in the broader professional community."[16] Thus, improvements in the profession's knowledge will not necessarily improve an individual physician's knowledge. These problems are not intractable: The

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11. *Id.* at 181 (adding, however, that this discursive community obviously has significant ties to the sciences); *see also id.* at 51–52 (enumerating the different sites for medical discourse); *id.* at 162–64 (proposing an archeological account of medical discourse); KARIN KNORR CETINA, EPISTEMIC CULTURES: HOW THE SCIENCES MAKE KNOWLEDGE 29–32 (1999); *cf.* J.A. Muir Gray, *Postmodern Medicine*, 354 LANCET 1550, 1550–52 (1999) (explaining that medicine straddles the line between modernist optimism about finding objective truths and postmodern skepticism).

12. *See* MICHEL FOUCAULT, THE BIRTH OF THE CLINIC: AN ARCHAEOLOGY OF MEDICAL PERCEPTION 28–31, 54–57, 96–97, 136–37 (A.M. Sheridan Smith trans., Pantheon Books 1973).

13. *See* David L. Sackett et al., Editorial, *Evidence Based Medicine: What It Is and What It Isn't*, 312 BRIT. MED. J. 71, 71 (1996).

14. *See* JAY KATZ, THE SILENT WORLD OF DOCTOR AND PATIENT 166 (1984) ("Medical knowledge is engulfed and infiltrated by uncertainty."); Eric B. Beresford, *Uncertainty and the Shaping of Medical Decisions*, HASTINGS CTR. REP., July–Aug. 1991, at 6, 8 ("Uncertainty will not be eliminated by any degree of technological advance; indeed,...it may be exacerbated by such advance."); David M. Eddy, *Variations in Physician Practice: The Role of Uncertainty*, HEALTH AFF., Summer 1984, at 74, 75 ("Uncertainty creeps into medical practice through every pore."); Renée C. Fox, *The Evolution of Medical Uncertainty*, 58 MILBANK Q. 1, 43–45 (1980).

15. ERIC J. CASSELL, DOCTORING: THE NATURE OF PRIMARY CARE MEDICINE 70 (1997) (suggesting a pair of additional and ultimately intractable causes of uncertainty in making clinical judgments: they require making predictions about the future, and they concern the peculiarities of individual patients).

16. William M. Sage, *Regulating Through Information: Disclosure Laws and American Health Care*, 99 COLUM. L. REV. 1701, 1774 (1999); *see also* Alexander Morgan Capron, *Does Assessment of Medical Practices Have a Future?*, 82 VA. L. REV. 1623, 1623 (1996) ("It is striking that medicine—for all its vaunted love of the scientific method and the biomedical technologies that are the fruits of scientific investigation—has long been remarkably uninterested in systematically studying the effectiveness of much of what the health care system provides to patients.").

biomedical research community can do a better job of generating and disseminating information, and physicians can do a better job of digesting such research while doing their best to manage any residual uncertainties. This Article will elaborate on both of these points.

Knowledge and information are not synonymous. People must absorb information in order to learn and become knowledgeable,[17] and then their expertise provides the occasion for applying knowledge in appropriate circumstances.[18] Psychologists recognize that individuals often encounter difficulties in processing information, which leads to a reliance on various "heuristics."[19] Physicians are no different; they also struggle when processing large amounts of complex information and fall back on heuristics when making decisions.[20]

This Article addresses the application of biomedical research to clinical practice. Its locus of inquiry differs from the normal scholarly emphasis on the

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17. *See* JOHN SEELY BROWN & PAUL DUGUID, THE SOCIAL LIFE OF INFORMATION 119–29 (2000). Others argue, however, that technological changes have blurred this distinction:

> Increasingly, *knowledge* is used synonymously with *information*, and learning is less a matter of studying and memorizing things than it is of knowing how to access information from available sources efficiently and effectively. Physicians, working in a field where scientific knowledge and the state-of-the-art change rapidly, will be especially affected by this....

Arnold J. Rosoff, *Informed Consent in the Electronic Age*, 25 AM. J.L. & MED. 367, 369 (1999).

18. *See* MICHAEL POLANYI, PERSONAL KNOWLEDGE: TOWARDS A POST-CRITICAL PHILOSOPHY 62–65, 373–76 (1958).

19. *See* Howard Latin, *"Good" Warnings, Bad Products, and Cognitive Limitations*, 41 UCLA L. REV. 1193, 1229–41 (1994) (describing the so-called representativeness, availability, framing, and anchoring heuristics); Roger G. Noll & James E. Krier, *Some Implications of Cognitive Psychology for Risk Regulation*, 19 J. LEGAL STUD. 747, 750 (1990). *See generally* DANIEL KAHNEMAN ET AL., JUDGMENT UNDER UNCERTAINTY: HEURISTICS AND BIASES (1982).

20. *See* David A. Bergman & Robert H. Pantell, *The Impact of Reading a Clinical Study on Treatment Decisions of Physicians and Residents*, 61 J. MED. EDUC. 380, 380–81, 384–85 (1986); Donald M. Berwick et al., *When Doctors Meet Numbers*, 71 AM. J. MED. 991, 997 (1981); David M. Eddy, *The Challenge*, 263 JAMA 287, 288–90 (1990); H.J. Featherstone et al., *Distorted Learning from Unusual Medical Anecdotes*, 18 MED. EDUC. 155, 156–57 (1984); Chris Guthrie et al., *Inside the Judicial Mind*, 86 CORNELL L. REV. 777, 782–83 (2001) ("Empirical studies demonstrate that cognitive illusions plague assessments that many professionals, including doctors...and psychologists, make." (footnote omitted)); Clement J. McDonald, *Medical Heuristics: The Silent Adjudicators of Clinical Practice*, 124 ANNALS INTERNAL MED. 56 (1996) (explaining that physicians employ "rules of thumb" peculiar to medical practice); Donald A. Redelmeier & Eldar Shafir, *Medical Decision Making in Situations That Offer Multiple Alternatives*, 273 JAMA 302, 304–05 (1995); *see also* NICHOLAS CHRISTAKIS, DEATH FORETOLD: PROPHECY AND PROGRESS IN MEDICAL CARE 66–68 (2000); Anthony S. Dixon, *The Evolution of Clinical Policies*, 28 MED. CARE 201, 215–16 (1990); *infra* notes 104, 131–42 and accompanying text.

vertical transmission of information from physicians to patients in connection with the duty to secure informed consent.[21] Instead, this Article focuses on the more horizontal process by which health care professionals acquire and assimilate often incomplete and conflicting medical information. In an effort to better understand the diffusion of biomedical knowledge, it poses the following sorts of questions: How do physicians become knowledgeable? How rapidly do they become aware of new data, and how long do they cling to old habits and assumptions? How do health care professionals respond when research throws into question existing dogma? Even necessarily tentative answers to such questions could have profound ramifications for various policymakers.

Several institutions look to and, in turn, influence the diffusion of biomedical knowledge. The debate over evidence-based medicine (EBM) may have important lessons for a variety of legal issues involving medical practice and technology, but so far it has received little meaningful attention among legal scholars. This Article strives to bridge that gap in the literature. It does so, in part, by considering the production and dissemination of information about medical practices as compared with information about medical technologies. As it turns out, we already have evidence-based *medicines*, but we most certainly do not yet enjoy fully evidence-based medical practice. Such a disjunction between theory and practice may have serious consequences for patient welfare. First, however, this Article contrasts the ways in which judges and doctors review scientific evidence, and then it elaborates on the different types of biomedical knowledge and methods for its dissemination.

As detailed in Part II, biomedical knowledge may emerge from a variety of sources, ranging from personal experience and case reports published by other physicians to observational studies and controlled clinical trials. Proponents of EBM urge health care professionals to place greater reliance on the latter types of information, while many physicians retain confidence in anecdotalism. Part III catalogues and critically evaluates the different mechanisms used for

21. *See, e.g.*, PAUL S. APPELBAUM ET AL., INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE 156 (1987) ("[M]edical decision making is a continuous process, and the exchange of information must take place throughout the course of the physician-patient relationship."); RUTH R. FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT (1986); STEPHEN WEAR, INFORMED CONSENT: PATIENT AUTONOMY AND PHYSICIAN BENEFICENCE WITHIN HEALTH CARE (2d ed. 1998); Paula Berg, *Toward a First Amendment Theory of Doctor-Patient Discourse and the Right to Receive Unbiased Medical Advice*, 74 B.U. L. REV. 201 (1994); Michael A. Jones, *Informed Consent and Other Fairy Stories*, 7 MED. L. REV. 103 (1999); Joan H. Krause, *Reconceptualizing Informed Consent in an Era of Health Care Cost Containment*, 85 IOWA L. REV. 261, 269 (1999); Peter H. Schuck, *Rethinking Informed Consent*, 103 YALE L.J. 899 (1994); Mark Fajfar, Note, *An Economic Analysis of Informed Consent to Medical Care*, 80 GEO. L.J. 1941, 1950 (1992) ("By exchanging information, the patient and provider both expand their knowledge, thereby increasing the probability that the patient will choose an appropriate form of treatment."); *see also* Ben A. Rich, *Postmodern Medicine: Deconstructing the Hippocratic Oath*, 65 U. COLO. L. REV. 77, 93–99, 105–17 (1993) (discussing recent transformations in the doctor-patient relationship).

disseminating biomedical information, including medical conferences, professional journals, textbooks, practice guidelines, and industry advertising. Proponents of EBM favor systematic compilations of randomized controlled trials as a source of clinically relevant information, while physicians may rely excessively on promotional channels of communication.

Finally, Part IV elaborates on the various ways that legal institutions influence the production, dissemination, and assimilation of biomedical information. Federal regulatory agencies that supervise the commercialization of medical technologies require that sponsors undertake clinical trials of their drugs and devices and then communicate the results to health care professionals in a balanced fashion. Because no such regulatory regime governs surgery and other medical procedures, and because intellectual property protections fail to create comparable incentives to conduct research in this field, a serious imbalance exists in the database available for competing therapeutic options. In supervising products liability and medical malpractice litigation, the courts also play a role in the process, and the doctrinal differences between these two fields of tort law exacerbate the asymmetry in the information base. Greater attention to the insights of EBM may facilitate the resolution of tort litigation involving medical technologies and medical practice. In turn, the courts may help to encourage the production of biomedical research and perhaps also persuade physicians to align their practice patterns more closely with the ideals of evidence-based medicine.

II. THE NATURE OF BIOMEDICAL KNOWLEDGE

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*,[22] the United States Supreme Court undertook to interpret the reference in Federal Rule of Evidence 702 to "scientific...knowledge."[23] Citing a dictionary, the Court explained that "the word 'knowledge' connotes more than subjective belief or unsupported speculation. The term applies to any body of known facts or to any body of ideas inferred from such facts or accepted as truths on good grounds."[24] The Court emphasized, however, that "there are important differences between the quest for

22. 509 U.S. 579 (1993).

23. FED. R. EVID. 702 ("If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise."). Effective Dec. 1, 2000, an amendment to the Rule inserts at the end the following new text: ", if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case." 192 F.R.D. 340, 418 (2000).

24. *Daubert*, 509 U.S. at 590 (citing WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY OF THE ENGLISH LANGUAGE, UNABRIDGED 1252 (1986)). The Court added that the latitude granted experts under Rules 702 and 703, which allows a witness to base testimony on otherwise inadmissible evidence, "is premised on an assumption that the expert's opinion will have a reliable basis in the knowledge and experience of his discipline." *Id.* at 592.

truth in the courtroom and the quest for truth in the laboratory. Scientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly."[25] Perhaps one should make the same point about the quest for truth at the bedside insofar as physicians must treat patients while operating under a variety of constraints, not the least of which is inadequate information.

In a subsequent article concerning scientific expert testimony, one commentator described "law's epistemology" as concerned with the rules of evidence and procedure governing such questions as admissibility, relevance, and materiality.[26] Modern medicine has its own distinctive epistemology, which relates to the procedures and conventions of biomedical research (e.g., design of clinical trials and editorial peer review) as well as the way that the findings of such research become translated into practice (e.g., continuing medical education programs and the development of clinical practice guidelines). The Supreme Court previously had suggested that, "[w]ithin the medical discipline, the traditional standard for 'factfinding' is a 'reasonable medical certainty.'"[27] As this Article will try to explain, an "educated guess" might come closer to the mark. Even if the judiciary's expectations about reasonable medical certainty represent something of a misunderstanding about clinical decisionmaking, courts have long made such an assumption when evaluating the testimony of physicians.[28]

The Supreme Court recently extended *Daubert*'s criteria for screening expert testimony to those with technical or other specialized knowledge drawn from training and experience.[29] Lower courts have, however, struggled when

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25. *Id.* at 596–97; *see also* D.H. Kaye, *Proof in Law and Science*, 32 JURIMETRICS J. 313, 317–18 (1992).

26. *See* Scott Brewer, *Scientific Expert Testimony and Intellectual Due Process*, 107 YALE L.J. 1535, 1540–42 (1998); *see also* Alani Golanski, *Why Legal Scholars Get* Daubert *Wrong: A Contextualist Explanation of Law's Epistemology*, 22 WHITTIER L. REV. 653, 672–75, 694–705 (2001) (criticizing Brewer's broader argument that laypersons cannot sensibly select among contested scientific claims, and emphasizing that legal institutions have adequate mechanisms for evaluating these questions for their own more limited dispute resolution purposes than trying ultimately to settle scientific controversies).

27. Addington v. Texas, 441 U.S. 418, 430 (1979) (discussing what burden of proof to apply to psychiatric testimony in civil commitment proceedings).

28. *See* Jeff L. Lewin, *The Genesis and Evolution of Legal Uncertainty About 'Reasonable Medical Certainty,'* 57 MD. L. REV. 380, 397–406 (1998); *see also id.* at 401 (adding that "the concept of certainty is just as elusive in medicine as in other scientific disciplines, if not more so"); *id.* at 499 (suggesting that use of the phrase, starting early in the twentieth century, "implicitly embraced the prevailing view of medical science as an exogenous source of objective and fixed truths in a rapidly modernizing and increasingly uncertain world"); *id.* at 490–93 (explaining that in recent years many legislatures have codified this standard in various contexts).

29. *See* Kumho Tire Co. v. Carmichael, 526 U.S. 137, 147–57 (1999) (applying *Daubert* to the testimony of an engineer that was based on his experience and observation rather than scientific research on tire failures); *see also* Edward J. Imwinkelried, *The Next Step After* Daubert*: Developing a Similarly Epistemological Approach to Ensuring the Reliability of Nonscientific Expert Testimony*, 15 CARDOZO L. REV. 2271, 2276 (1994)

asked to apply *Daubert* to testimony offered by physicians,[30] which reflects some ambiguity about exactly what type of knowledge clinicians have and can offer at trial. When physicians testify in toxic tort cases as to the probable cause of a particular injury, courts may focus on the thoroughness of the differential diagnosis,[31] assuming that this process of elimination has some reliable basis for making judgments about etiology.[32]

Consider another recent controversy that turned on the judiciary's perhaps unreflective views about the character of knowledge in the biomedical community. The Food and Drug Administration (FDA) strictly regulates the advertising of prescription pharmaceuticals. Among other things, the agency restricts the circumstances in which manufacturers may distribute to physicians medical textbooks and reprints of articles that discuss unapproved uses of approved drugs.[33] In resolving a First Amendment challenge to this restriction, a federal judge invalidated the rules after concluding that the government lacks any substantial interest in preventing the dissemination of potentially misleading

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("The common law courts embraced Locke's premise that experience is the best and most 'solid basis for human knowledge,'" but they expressed "skepticism about opinions such as scientific testimony." (footnote omitted)); *id.* at 2291 ("[O]ne of the most fundamental tests of the reliability of nonscientific opinion is whether it has any supporting experience, either personal or vicarious. David Hume, who was one of Locke's successors, noted that the trustworthiness of an inference depends upon 'a repetition of similar' experiences."); Joseph Sanders, Kumho *and How We Know*, LAW & CONTEMP. PROBS., Spring–Summer 2001, at 373, 387–92, 401–04.

30. *Compare* Moore v. Ashland Chem., Inc., 151 F.3d 269, 275 n.6 (5th Cir. 1998) (en banc) (applying *Daubert*), *and In re* Breast Implant Litig., 11 F. Supp. 2d 1217, 1230 (D. Colo. 1998) (same), *with* Westberry v. Gislaved Gummi A.B., 178 F.3d 257 (4th Cir. 1999) (holding that *Daubert* does not strictly apply to medical diagnosis), Heller v. Shaw Indus., Inc., 167 F.3d 146, 155–58 (3d Cir. 1999) (same), *and* Reese v. Stroh, 907 P.2d 282, 286 (Wash. 1995). *See generally* Jean Macchiaroli Eggen, *Clinical Medical Evidence of Causation in Toxic Tort Cases: Into the Crucible of* Daubert, 38 HOUS. L. REV. 369, 394–409 (2001); Gary Sloboda, *Differential Diagnosis or Distortion?*, 35 U.S.F. L. REV. 301 (2001).

31. *See* FED. R. EVID. 702 advisory committee's note, 192 F.R.D. at 419, 421; *see also* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 442–46, 479 (2d ed. 2000) ("It is challenging to...make explicit the extensive knowledge base and reasoning process that physicians implicitly employ in evaluating medical problems. Further work in this area will improve the transferability of medical knowledge into the courts and other arenas."). Thus, although the revision notes appear to endorse the Supreme Court's approach in *Daubert* and extend it to physician testimony, they also clarify that epidemiological studies are not essential predicates for admissibility.

32. In contrast, when physicians testify in a malpractice case as to what constitutes customary medical practice, *Daubert* would not seem to apply to this more purely descriptive form of expert testimony. *See* Mitchell v. United States, 141 F.3d 8, 14–17 (1st Cir. 1998); *see also* Carroll v. Morgan, 17 F.3d 787, 789–90 (5th Cir. 1994) (holding that an expert on the standard of care satisfied *Daubert* even though he failed to recognize any textbook or journal articles as authoritative); *infra* Part IV.B.2 (discussing malpractice litigation).

33. *See infra* Part IV.A.2.

information to physicians.[34] The court essentially took judicial notice of the fact that doctors can and do critically evaluate information concerning therapeutic advances. This confident assumption is hardly self-evident, but it pervades decisions by regulatory agencies as well as the courts when they resolve products liability and medical malpractice litigation. If, in fact, physicians experience difficulties assimilating biomedical information, then decisionmakers may have to rethink their approach in a variety of health care contexts.

Whether or not the courts will manage to comprehend the limitations of expert testimony offered by physicians, leaders in the biomedical community have begun to urge health care professionals to take into account the shortcomings of their own knowledge-base when treating patients. By constructing a rough hierarchy that reflects the value of the different types of clinically-relevant information, evidence-based medicine attempts to improve decisionmaking by practicing physicians.[35] When faced with a clinical problem, health care professionals should, in descending order of preference, look for guidance in systematic reviews of randomized controlled trials, the results of individual controlled clinical trials, observational (uncontrolled) studies, and anecdotal reports of clinical observations.[36] The sections that follow elaborate on each of these different types of biomedical information. Personal clinical experience remains an essential predicate for the effective application of EBM,[37] but it should not provide the primary basis for making treatment decisions.[38]

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34. *See* Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 70 (D.D.C. 1998), *order amended*, 36 F. Supp. 2d 16, 19 (D.D.C. 1999), *order amended sub nom.* Washington Legal Found. v. Henney, 56 F. Supp. 2d 81, 87 (D.D.C. 1999), *vacated in part and appeal dismissed*, 202 F.3d 331 (D.C. Cir. 2000).

35. *See* Gordon H. Guyatt et al., *Users' Guides to the Medical Literature: XXV. Evidence-Based Medicine: Principles for Applying the Users' Guides to Patient Care*, 284 JAMA 1290, 1291 (2000) ("An evidence-based practitioner must be able...to identify knowledge gaps, and frame questions to fill those gaps; to conduct an efficient literature search; to critically appraise the research evidence; and to apply that evidence to patient care."); Cynthia D. Mulrow & Kathleen N. Lohr, *Proof and Policy from Medical Research Evidence*, 26 J. HEALTH POL., POL'Y & L. 249, 252–58 (2001).

36. *See* Guyatt et al., *supra* note 35, at 1292–93 ("The hierarchy implies a clear course of action for physicians addressing patient problems–they should look for the highest available evidence from the hierarchy.").

37. *See id.* at 1293 ("[K]nowing the tools of evidence-based practice is necessary but not sufficient for delivering the highest-quality patient care."); Sackett, *supra* note 13, at 72. Proponents of EBM emphasize the importance of individualizing whatever evidence exists to account for variability in each patient's condition and preferences. *See* Finlay A. McAlister et al., *Users' Guides to the Medical Literature: XX. Integrating Research Evidence with the Care of the Individual Patient*, 283 JAMA 2829, 2830 (2000); *see also* Paul Cotton, *Examples Abound of Gaps in Medical Knowledge Because of Groups Excluded from Scientific Study*, 263 JAMA 1051 (1990).

38. *See* Guyatt et al., *supra* note 35, at 1293 ("The evidence may be extremely weak—the unsystematic observation of a single clinician, or generalization from only indirectly related physiologic studies—but there is always evidence."); David L. Sackett &

EBM has instructive parallels to the shift in the judiciary's approach to scientific expert testimony.[39] Physicians (like judges) must make decisions in the face of uncertainty and without scientists' luxury of awaiting further information. Traditionally, when unsure about how to proceed, physicians would look to the judgments of "opinion leaders" in their community for guidance, somewhat akin to the old "general acceptance" standard used by the courts.[40] With the rapid expansion of the research literature and the growing fragmentation of expert communities, this consensus-based approach lost some of its former appeal. Because of escalating concerns that medical practice lacked a firm scientific basis (though no one has yet complained of "junk medicine"), commentators began to urge physicians to become more adept at accessing and interpreting the biomedical literature; EBM, like *Daubert*, calls for improved gatekeeping by generalist decisionmakers using cues from the research community in the hopes of securing more credible results.[41] In turn, both efforts have encountered some criticism for adopting overly rigid definitions of what qualifies as the best evidence for making particular decisions.

A. Anecdotes, Experience, and Epidemiology

Traditionally, physicians relied heavily on personal experience and anecdotal information. Although medical students must absorb enormous quantities of information,[42] their most meaningful learning occurs only after

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John E. Wennberg, Editorial, *Choosing the Best Research Design for Each Question: It's Time to Stop Squabbling over the "Best" Methods*, 315 BRIT. MED. J. 1636 (1997).

39. *See* Daniel W. Shuman, *Expertise in Law, Medicine, and Health Care*, 26 J. HEALTH POL., POL'Y & L. 267, 287 (2001) ("Science-based medical evidence and the *Daubert* trilogy reflect unorchestrated parallel movements in medicine and law about how to assess expertise critically.").

40. *See* Frye v. United States, 293 F. 1013, 1014 (D.C. 1923). The Supreme Court held that Rule 702 had displaced *Frye*, *see* Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 585–89 (1993), but then it made general acceptance one of the factors that judges should use in making admissibility determinations, *see id.* at 594.

41. *See* John M. Eisenberg, *What Does Evidence Mean? Can the Law and Medicine Be Reconciled?*, 26 J. HEALTH POL., POL'Y & L. 369, 372 (2001) (noting that the traditional "difference in the way in which evidence is approached creates a cultural divide between medicine and the law, a conflict with its roots in different epistemologies of evidence," but suggesting that *Daubert* "moved in the direction of reconciling" these differences); *id.* at 377 ("[T]he decision about whether research findings are worthy of publication is a key step in the creation of the evidentiary base for clinical practice."); Michelle M. Mello & Troyen A. Brennan, *Demystifying the Law/Science Disconnect*, 26 J. HEALTH POL., POL'Y & L. 429, 434 (2001) (noting that, like a judge making admissibility determinations, physicians "must rely on a variety of different types of studies, with little training in how to weigh that evidence and apply it to the clinical setting"). Of course, physicians are more active, though largely unaided, information seekers than trial judges; conversely, their treatment decisions are more opaque and less readily scrutinized by others.

42. *See* J. Anderson & A. Graham, *A Problem in Medical Education: Is There an Information Overload?*, 14 MED. EDUC. 4, 7 (1980); Richard I. Cook, *Learning Theories Implicit in Medical School Lectures*, 261 JAMA 2244, 2244 (1989).

graduation. With practical experience comes judgment and intuition.[43] This process of maturation is inevitable and largely desirable, but the passage of time also can result in a stubborn and unreflective adherence to well-entrenched habits.[44] The conceit that doctors know best, or at least have a better handle on treating patients in the real world than do ivory tower research scientists, is surprisingly resilient: "In reviewing physician responses to questions regarding their sources of information on new technologies, the universal skepticism of practicing physicians regarding the utility of the scientific literature is startling."[45]

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43. *See* Abigail Zuger, *Teaching Old Dogs New Medicine Can Be Some Trick*, N.Y. TIMES, Mar. 13, 2001, at D5 ("In medical school, information streams out from the podium unimpeded, with nothing between student and education but some fancy memory work. Once out in the real world, though,...is where the real education begins."); *see also* KATHRYN MONTGOMERY HUNTER, DOCTORS' STORIES: THE NARRATIVE STRUCTURE OF MEDICAL KNOWLEDGE 27–40 (1991); Donald M. Berwick, Editorial, *Harvesting Knowledge from Improvement*, 275 JAMA 877, 878 (1996); David C. Leach, Editorial, *Competence Is a Habit*, 287 JAMA 243 (2002); Y.D. van Leeuwen et al., *Change in Knowledge of General Practitioners During Their Professional Careers*, 12 FAM. PRAC. 313 (1995).

44. *See* Eisenberg, *supra* note 41, at 369–70 ("[M]ost clinicians' practices do not reflect the principles of [EBM] but rather are based on tradition, their most recent experience, what they learned years ago in medical school, or what they have heard from their friends."); Paul G. Ramsey et al., *Changes over Time in the Knowledge Base of Practicing Internists*, 266 JAMA 1103, 1107 (1991); Sage, *supra* note 16, at 1774 ("[P]rofessional training socializes physicians to be almost compulsively individualistic, committed in the abstract to the ideals of science but in operation to practicing medicine idiosyncratically."); *see also* Barak Gaster, *The Learning Curve*, 270 JAMA 1280 (1993) (relating a story of one experienced surgeon's difficulties with a new laparoscopic procedure); Flora Haayer, *Rational Prescribing and Sources of Information*, 16 SOC. SCI. & MED. 2017, 2021–22 (1982).

45. Ann Lennarson Greer, *The State of the Art Versus the State of the Science: The Diffusion of New Medical Technologies into Practice*, 4 INT'L J. TECH. ASSESSMENT IN HEALTH CARE 5, 9 (1988); *see also* Gary S. Belkin, *The New Science of Medicine*, 19 J. HEALTH POL., POL'Y & L. 801, 802, 808 (1994) (conceding that "potentially dangerous and risky procedures were advocated on little more than anecdote and fashion," but ultimately "emphasizing an important role for the generation of knowledge in specific patient encounters"); Kathryn Montgomery Hunter, *'There Was This One Guy...': The Uses of Anecdotes in Medicine*, 29 PERSP. IN BIO. & MED. 619, 629–30 (1986); Rebecca K. Schwartz et al., *Physician Motivations for Nonscientific Drug Prescribing*, 28 SOC. SCI. & MED. 577, 579, 581 (1989) ("How can we understand the fact that over a quarter of the reasons for nonscientific prescribing stemmed from a deep skepticism about clinical trials, from a belief that clinical experience, rather than scientific evidence, should govern clinical practice?"); Sandra J. Tanenbaum, *Knowing and Acting in Medical Practice: The Epistemological Politics of Outcomes Research*, 19 J. HEALTH POL., POL'Y & L. 27, 34–40 (1994); Amy L. Wax, *Technology Assessment and the Doctor-Patient Relationship*, 82 VA. L. REV. 1641, 1644 (1996) (recognizing that "[t]he model of individualized care...[has] potentially serious drawbacks and temptations (such as its ever-present invitation to an unrigorous anecdotal approach)"); *id.* at 1648 ("[I]n actual medical practice, [choices] are often based not on accurate information but on intuition, prejudice, anecdote, or unsubstantiated lore.").

EBM represents a response to the shortcomings of this idiosyncratic, "opinion-based" approach to medical practice.[46]

In some instances, individual experience can provide a fairly robust basis for making treatment decisions. For instance, physicians often titrate dosages of medications until they find a level that seems to work best for their particular patient, or they may try a variety of alternatives until hitting upon the one that seems most effective. Some researchers have glorified this simple trial-and-error approach as a randomized controlled trial (RCT) with a sample size (N) of one, at least when physicians provide their patients with alternative treatments (or perhaps a placebo) for a chronic condition during distinct time periods in order to compare the results.[47] Such "N of 1" trials may offer important advantages over large-scale RCTs, which can only offer generalizations that may fail to account for the significant variability among patients.[48] In practice, however, physicians rarely manage to undertake a genuinely controlled trial when treating individual patients.[49]

Anecdotal experience may cumulate, becoming a more valuable source of information in the process. For example, reports of isolated adverse events may,

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46. *See* Frank Davidoff et al., Editorial, *Evidence-Based Medicine: Why All the Fuss?*, 122 ANNALS INTERNAL MED. 727, 727 (1995) ("'Authoritarian medicine' may thus be gradually yielding to 'authoritative medicine.'"); Eisenberg, *supra* note 41, at 370 (explaining that EBM seeks to displace the tradition of "opinion-based" and "eminence-based" medical practice); William Rosenberg & Anna Donald, *Evidence-Based Medicine: Approach to Clinical Problem-Solving*, 310 BRIT. MED. J. 1122 (1995).

47. *See* Gordon Guyatt et al., *Determining Optimal Therapy: Randomized Trials in Individual Patients*, 314 NEW ENG. J. MED. 889 (1986); Gordon H. Guyatt et al., *The N-of-1 Randomized Controlled Trial: Clinical Usefulness*, 112 ANNALS INTERNAL MED. 293, 297–98 (1990); Eric B. Larson et al., *Randomized Clinical Trials in Single Patients During a 2-Year Period*, 270 JAMA 2708, 2712 (1993).

48. *See* ERIC J. CASSELL, THE NATURE OF SUFFERING AND THE GOALS OF MEDICINE 179–81 (1991); Antonio L. Dans et al., *Users' Guides to the Medical Literature: XIV. How to Decide on the Applicability of Clinical Trial Results to Your Patient*, 279 JAMA 545 (1998); Jerome P. Kassirer, *Clinical Problem-Solving*, 326 NEW ENG. J. MED. 60, 60 (1992) ("Controlled studies guide us in the right direction, but only occasionally do patients match the study population precisely. The art of medicine involves interpolating between data points...."); Tanenbaum, *supra* note 45, at 33 ("Every doctor accumulates a vast and idiosyncratic knowledge of medicine. Furthermore, treating physicians must generalize and (especially) particularize their knowledge to suit their patients."); *see also* Barbara A. Noah, *Racial Disparities in the Delivery of Health Care*, 35 SAN DIEGO L. REV. 135, 153 & n.68 (1998) (noting significant racial and ethnic variations in drug metabolism that clinical trials often fail to take into account); *infra* Part II.B (elaborating on RCTs).

49. *See* Jeffrey Mahon et al., *Randomised Study of N of 1 Trials Versus Standard Practice*, 312 BRIT. MED. J. 1069, 1072 (1996) ("[D]espite endorsements of the technique, n of 1 trials are rarely used. This is probably because of the extra effort they demand...."). When a patient experiences an adverse reaction to treatment, a physician may use a "dechallenge/rechallenge" procedure to determine whether the treatment really caused the side effect, *see* Glastetter v. Novartis Pharm. Corp., 252 F.3d 986, 990–91 (8th Cir. 2001), but this approach differs from an N-of-1 RCT designed to gauge efficacy.

when considered in the aggregate, provide clues about potential safety problems.[50] In addition, "outcomes research" assembles data about large numbers of similar patients in an effort to assess the effectiveness of particular therapeutic interventions under real world conditions.[51] As one of the first proponents of health care outcomes research proclaimed: "Such an approach allows the experiences of many physicians to be pooled, so that the individual physician does not have to rely exclusively on his own experience."[52] For instance, one recently published study found that heart catheterization solely for purposes of monitoring a patient during surgery, a practice that had became increasingly common over the course of the last thirty years, has no benefit and may even be counterproductive.[53] But how long will it take before surgeons get the message, and will some of them simply dismiss it because they think that they know better based on their own successful experiences in using this procedure?

Outcomes research has attracted its share of critics. Some detractors complain that this form of research lacks the rigor of more carefully structured

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50. *See* Michael A. Friedman et al., *The Safety of Newly Approved Medicines: Do Recent Market Withdrawals Mean There Is a Problem?*, 281 JAMA 1728, 1728 (1999) (describing a report from Mayo Clinic researchers of twenty-four cases of valvular disease and aortic and mitral valve regurgitation in patients taking fenfluramine in combination with the amphetamine phentermine); Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, 49 CATH. U. L. REV. 449, 456 n.24 (2000) ("In a sense, the FDA's formal system of monitoring and reporting is supplemented by an informal discourse within the medical community about the apparent side effects associated with newly-marketed drugs.").

51. *See* Arnold M. Epstein, *The Outcomes Movement—Will It Get Us Where We Want to Go?*, 323 NEW ENG. J. MED. 266, 267 (1990); Ralph I. Horwitz et al., *Developing Improved Observational Methods for Evaluating Therapeutic Effectiveness*, 89 AM. J. MED. 630, 636–37 (1990); Arnold S. Relman, *Assessment and Accountability: The Third Revolution in Medical Care*, 319 NEW ENG. J. MED. 1220 (1988); *see also* Wax, *supra* note 45, at 1651 ("Technology assessment allows conscientious physicians to think through the possible approaches to diagnosis and treatment in a systematic and informed manner, rather than relying on intuition, anecdote and limited personal experience.").

52. Alain C. Enthoven, *Shattuck Lecture—Cutting Cost Without Cutting the Quality of Care*, 298 NEW ENG. J. MED. 1229, 1236 (1978) (adding that it "can be debated and corrected much more easily than an intuitive, implicit analysis"); *see also* Paul M. Ellwood, *Shattuck Lecture-Outcomes Management: A Technology of Patient Experience*, 318 NEW ENG. J. MED. 1549, 1554 (1988) ("Doctors will find that they need to depend less on their memories,...that the statistics on which they base decisions will be more robust, and that the recommendations of their colleagues can be cross-checked."); *id.* at 1550 ("[T]he health care system has become an organism...desperately in need of a central nervous system that can help it cope with the complexities of modern medicine.").

53. *See* Carisi A. Polanczyk et al., *Right Heart Catheterization and Cardiac Complications in Patients Undergoing Noncardiac Surgery: An Observational Study*, 286 JAMA 309 (2001). For an example of an outcomes study documenting the therapeutic benefit of a simple procedure, see Wen-Chih Wu et al., *Blood Transfusion in Elderly Patients with Acute Myocardial Infarction*, 345 NEW ENG. J. MED. 1230 (2001).

studies.[54] In addition, the enthusiasm for such investigations has generated something of a backlash by those who object to what they view as reductionism and instead emphasize the primacy of craft knowledge.[55] Outcomes research, like the EBM movement more generally, may alter the locus of decisionmaking power in the health care community, threatening the traditional hegemony of physicians while empowering statisticians and managers.[56]

Epidemiological studies, which track and compare large groups of individuals over extended periods of time, represent the most structured method for reviewing accumulated experience.[57] Researchers may undertake epidemiological studies in response to anecdotal reports that suggest an association between an adverse health effect and a therapeutic intervention, dietary practice, or exposure to a suspected toxin.[58] For example, recently published

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54. *See* Christopher Anderson, *Measuring What Works in Health Care*, 263 SCIENCE 1080 (1994).

55. *See* Belkin, *supra* note 45, at 804 (complaining that outcomes research "reframes socially contingent craft knowledge as universally accessible objective and quantified knowledge"); *id.* at 802–03 ("They ignore the uncertainty and contingency of medical knowledge."); *id.* at 807 ("The elusive nature of science and fact, experience and hypothesis testing that is medicine is less a science than a way to encounter illness. In that respect it, when done well, does more for humanity than can be collected as data."); David Grahame-Smith, *Evidence-Based Medicine: Socratic Dissent*, 310 BRIT. MED. J. 1126 (1995); Sandra J. Tanenbaum, *What Physicians Know*, 329 NEW ENG. J. MED. 1268, 1269–70 (1993); *see also* Warren Newton, *Rationalism and Empiricism in Modern Medicine*, LAW & CONTEMP. PROBS., Autumn 2001, at 299, 305 ("What is going on in medicine now is a war of cultures between those for whom the mechanisms of disease constitute the best kind of evidence and those who think that appropriately analyzed outcomes are critical."); *id.* at 314 ("For all its rhetoric of novelty, [EBM] represents a counter-revolution of traditional empiricism, draped in modern clothes of statistics and multi-variate analysis."). *See generally* Deborah R. Gordon, *Clinical Science and Clinical Expertise: Changing Boundaries Between Art and Science in Medicine*, *in* BIOMEDICINE EXAMINED 257 (Margaret Lock & Deborah Gordon eds., 1988).

56. *See* Marc A. Rodwin, *The Politics of Evidence-Based Medicine*, 26 J. HEALTH POL., POL'Y & L. 439, 440–41 (2001); *cf.* Alastair McColl et al., *General Practitioners' Perceptions of the Route to Evidence-Based Medicine: A Questionnaire Survey*, 316 BRIT. MED. J. 361 (1998) (finding guarded enthusiasm about EBM among clinicians in England).

57. *See* Allison v. McGhan Med. Corp., 184 F.3d 1300, 1316 (11th Cir. 1999) ("While we acknowledge the importance of anecdotal studies for raising questions and comparing clinicians' findings, in the face of controlled, population-based epidemiological studies which find otherwise, these case studies pale in comparison."); Haggerty v. Upjohn Co., 950 F. Supp. 1160, 1165 (S.D. Fla. 1996) (explaining that case reports are "no substitute for a scientifically designed and conducted inquiry"), *aff'd mem.*, 158 F.3d 588 (11th Cir. 1998). *See generally* KENNETH J. ROTHMAN & SANDER GREENLAND, MODERN EPIDEMIOLOGY (2d ed. 1998).

58. *See* Mitchell Levine et al., *Users' Guides to the Medical Literature: IV. How to Use an Article About Harm*, 271 JAMA 1615, 1616–17 (1994); Lawrence K. Altman, *Risk of Death Found in Use of Heart Drug*, N.Y. TIMES, Nov. 1, 1995, at A16. For a few recent examples, see Nicole Glaser et al., *Risk Factors for Cerebral Edema in Children with Diabetic Ketoacidosis*, 344 NEW ENG. J. MED. 264 (2001); Mona Lydon-Rochelle et al.,

research has refuted a widely publicized claim-based largely on anecdotal reports-that certain childhood vaccines may trigger autism.[59] Epidemiological studies suffer from a number of shortcomings, however, that may limit their usefulness as a source of definitive information.[60] Nonetheless, like other forms of outcomes research, epidemiological studies offer a better foundation for making treatment decisions than the traditional tendency among physicians to rely on their numerically far more limited direct encounters with comparable patients. In the event that a pediatrician saw a couple of children who happened to develop autism within days of an MMR inoculation, cognitive psychologists would predict an inclination to give exaggerated weight to that information, but surely the pediatrician could not justify a decision to stop vaccinating patients in light of the reassuring epidemiological findings.

B. Controlled Clinical Trials

Randomized controlled trials (RCTs) represent the "gold standard" for biomedical research,[61] and manufacturers of most new medical technologies must perform such clinical trials in order to generate the data required for FDA approval.[62] Although clinical experience may provide a basis for selecting therapeutic interventions, especially when buttressed by observational (uncontrolled) studies that cumulate such experience, only controlled human trials can provide firm evidence for making therapeutic judgments. RCTs discredit long-

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Risk of Uterine Rupture During Labor Among Women with a Prior Cesarean Delivery, 345 NEW ENG. J. MED. 3 (2001); Gunnar Lauge Nielson et al., *Risk of Adverse Birth Outcome and Miscarriage in Pregnant Users of Non-Steroidal Anti-Inflammatory Drugs*, 322 BRIT. MED. J. 266 (2001).

59. *See* Bruce G. Gellin & William Schaffner, Editorial, *The Risk of Vaccination—The Importance of 'Negative" Studies*, 344 NEW ENG. J. MED. 372, 372 (2001).

60. *See* Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of* Agent Orange *and Bendectin Litigation*, 86 NW. U. L. REV. 643, 648–53 (1992); Gary Taubes, *Epidemiology Faces Its Limits*, 269 SCIENCE 164, 164 (1995) ("[M]any epidemiologists concede that their studies are so plagued with biases, uncertainties, and methodological weaknesses that they may be inherently incapable of accurately discerning such weak associations.").

61. *See* ROBERT J. LEVINE, THE ETHICS AND REGULATION OF CLINICAL RESEARCH 211 (2d ed. 1986) ("[T]he RCT is the *gold standard* for evaluating therapeutic efficacy."); Michael Clarke & Iain Chalmers, *Discussion Sections in Reports of Controlled Trials Published in General Medical Journals: Islands in Search of Continents?*, 280 JAMA 280, 280 (1998) ("No other category of biomedical report has received such sustained attention, and this reflects the practical importance of controlled trials in guiding decisions in health care."). *See generally* STUART J. POCOCK, CLINICAL TRIALS: A PRACTICAL APPROACH (1983).

62. *See* 21 C.F.R. §§ 314.126(b)(2), 860.7(f)(1)(iv) (2001); Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1767, 1771, 1779–82 (1996); Robert Temple, *Government Viewpoint of Clinical Trials*, 16 DRUG INFO. J. 10, 11–13 (1982); *see also infra* notes 269–71 and accompanying text.

accepted medical treatments with disturbing regularity,[63] and they also sometimes cast doubts on the conclusions of observational studies.[64] For instance, after a series of conflicting results from epidemiological studies concerning a possible link between hormone replacement therapy and stroke in post-menopausal women, the publication of a large-scale controlled trial finding no association cut through some of the confusion.[65] Conversely, two other recently published RCTs of hormone replacement therapy contradicted previous findings from epidemiological studies suggesting that it protected women against heart disease and stroke.[66]

According to one frequently cited estimate, controlled trials exist to support the efficacy of less than twenty percent of therapeutic interventions.[67]

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63. *See* Wendy K. Mariner, *Outcomes Assessment in Health Care Reform: Promise and Limitations*, 20 AM. J.L. & MED. 37, 40 (1994) ("When properly studied, some commonly accepted medical procedures are found to be of no significant benefit.") (citing Richard Epstein et al., *Effects of Parenterally Administered Gold Therapy on the Course of Adult Rheumatoid Arthritis*, 114 ANNALS INTERNAL MED. 437 (1991)); *see also* Arthur Shafer, *The Ethics of the Randomized Clinical Trial*, 307 NEW ENG. J. MED. 719, 723 (1982) ("If a study of the history of medicine reveals anything, it reveals that clinical judgment without the check of scientific controls is a highly fallible compass."); Paul S. Swerdlow, Editorial, *A Tradition of Testing Ironclad Practices*, 267 JAMA 560, 561 (1992) (noting "the considerable burden of incorrect information with the status of lore"); Gina Kolata, *Questions Raised on Lung Operation*, N.Y. TIMES, Aug. 15, 2001, at A1 (describing the initial results of a government-sponsored RCT finding that a popular new surgical intervention for emphysema was ineffective and perhaps dangerous at least for the most critically ill patients).

64. *See* Gordon H. Guyatt et al., *Users' Guides to the Medical Literature: II. How to Use an Article About Therapy or Prevention: A. Are the Results of the Study Valid?*, 270 JAMA 2598, 2599 (1993); Regina Kunz & Andrew D. Oxman, *The Unpredictability Paradox: Review of Empirical Comparisons of Randomised and Non-Randomised Clinical Trials*, 317 BRIT. MED. J. 1185, 1188 (1998); Stuart J. Pocock & Diana R. Elbourne, Editorial, *Randomized Trials or Observational Tribulations?*, 342 NEW ENG. J. MED. 1907 (2000). *But cf.* Kjell Benson & Arthur J. Hartz, *A Comparison of Observational Studies and Randomized, Controlled Trials*, 342 NEW ENG. J. MED. 1878, 1884 (2000) (finding that they "usually produce similar results"); John P.A. Ioannidis et al., *Comparison of Evidence of Treatment Effects in Randomized and Nonrandomized Studies*, 286 JAMA 821, 827 (2001) (same).

65. *See* Denise Grady, *A New Look at Estrogen and Stroke*, N.Y. TIMES, Feb. 6, 2001, at D7.

66. *See* Susan Okie, *Hormones Don't Protect Women from Heart Disease*, WASH. POST, July 24, 2001, at A1; Rita Rubin, *Estrogen Isn't the Magic Pill: Study Shows HRT Doesn't Help Women Avoid Stroke*, USA TODAY, Oct. 25, 2001, at 10D. A related study found evidence of a different risk that had also previously been the subject of dispute. *See* Susan Okie, *Estrogen, Ovarian Cancer Linked*, WASH. POST, Mar. 21, 2001, at A1.

67. *See* U.S. OFFICE OF TECH. ASSESSMENT, ASSESSING THE EFFICACY AND SAFETY OF MEDICAL TECHNOLOGIES 7 (1978); Michael Dubinsky & John H. Ferguson, *Analysis of the National Institutes of Health Medicare Coverage Assessment*, 6 INT'L J. TECH. ASSESSMENT IN HEALTH CARE 480, 487 (1990) ("[I]n almost 80% of the assessments conducted at NIH, the reviewers had to rely on expert opinion because no controlled research evidence was available for their assessment.").

Although some researchers question the basis for this estimate and suggest that it is overly pessimistic,[68] no one denies that many medical treatments remain seriously understudied. A number of factors account for this data gap:

> [RCTs] are events of epic proportion, lasting for years, costing millions of dollars, involving thousands of patients, facing monumental bureaucratic barriers, and raising serious ethical issues. Often, by the time clinical trials are completed, the technology they studied is outmoded. Although other methodologies have been developed and can yield useful information, physicians must regularly weigh the preponderance of imperfect evidence in order to estimate whether a particular patient might benefit from a particular intervention.[69]

Resource constraints may present the main obstacle to concerted efforts at technology assessment.[70] Unless the government mandates (or sponsors) RCTs, or else creates special incentives for those interested in conducting such research, many treatment options will remain largely unexamined.[71]

Apart from insufficient economic incentives, ethical constraints may complicate efforts to conduct RCTs. Clinical trials often use placebos in the control group, but in some situations that may be inappropriate. For instance, in the case of surgical interventions, researchers rarely perform sham surgeries in order to have a placebo-controlled group of patients.[72] Similar difficulties may

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68. *See* Jonathan Ellis et al., *Inpatient General Medicine Is Evidence Based*, 346 LANCET 407, 407, 409 (1995) (pointing out that if, instead, one asks what portion of patients receive treatments supported by RCTs, the picture is far less gloomy); P. Gill et al., *Evidence Based General Practice: A Retrospective Study of Interventions in One Training Practice*, 312 BRIT. MED. J. 819, 819–21 (1996); Gaëtane Michaud et al., *Are Therapeutic Decisions Supported by Evidence from Health Care Research?*, 158 ARCHIVES INTERNAL MED. 1665, 1665–67 (1998).

69. Jan Blustein & Theodore R. Marmor, *Cutting Waste by Making Rules: Promises, Pitfalls, and Realistic Prospects*, 140 U. PA. L. REV. 1543, 1549 (1992) (footnotes omitted); *see also id.* ("While there is currently a great deal of enthusiasm about improving the scientific basis of medicine, and while there is surely room for improvement, a vast project to make medicine scientific can never keep up with innovations in medical practice."); David M. Eddy & John Billings, *The Quality of Medical Evidence: Implications for Quality of Care*, HEALTH AFF., Spring 1988, at 19, 28; Linda Rabeneck et al., *Problems in the Conduct and Analysis of Randomized Clinical Trials*, 152 ARCHIVES INTERNAL MED. 507, 511 (1992) (discussing problems that arise during the course of RCTs that make the results more difficult to interpret); John E. Wennberg, *Improving the Medical Decision-Making Process*, HEALTH AFF., Spring 1988, at 99 (referring to "an intellectual crisis in the scientific basis of clinical practice, which is of growing significance for medicine").

70. *See* H. DAVID BANTA & BRYAN R. LUCE, HEALTH CARE TECHNOLOGY AND ITS ASSESSMENT: AN INTERNATIONAL PERSPECTIVE 91–92, 283 (1993); Susan Bartlett Foote, *Assessing Medical Technology Assessment: Past, Present, and Future*, 65 MILBANK Q. 59, 75–76 (1987).

71. *See infra* note 328 and accompanying text.

72. *See* Thomas B. Freeman et al., *Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson's Disease*, 341 NEW ENG. J. MED. 988 (1999);

affect the ability to investigate the efficacy of medical devices,[73] even though spontaneous disease remission or the placebo effect may well account for reported improvements.[74] In any event, in the testing of surgical techniques or medical devices, one cannot readily "double-blind" a study so that even the investigator does not know whether the patient has received the experimental treatment or a control.

Aside from the peculiarities encountered in surgical settings, a placebo-controlled clinical trial designed to confirm the effectiveness of a well-accepted treatment would require depriving certain patients of any therapy. Similarly, a placebo-controlled clinical trial designed to evaluate an experimental treatment for a condition with an already established therapy would have the same effect. Some ethicists take the position that researchers generally should test new interventions against accepted therapies and reserve placebos only for those situations where no effective therapies currently exist.[75]

No one seriously defends the use of placebo controls when established therapies exist to treat serious and measurable conditions such as infections, diabetes, or cancer, where a placebo effect is less likely to explain favorable

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Ruth Macklin, *The Ethical Problems with Sham Surgery in Clinical Research*, 341 NEW ENG. J. MED. 992 (1999); Duncan Neuhauser, *Medical Technology Assessment as Social Responsibility*, 36 CASE W. RES. L. REV. 878, 882 & n.7 (1986); Marlene Cimons, *Fetal Cell Implants Improve Parkinson's Patients*, L.A. TIMES, Feb. 1, 2001, at A16; Magaret Talbot, *The Placebo Prescription*, N.Y. TIMES MAG., Jan. 9, 2000, at 34.

73. *See* Peter Barton Hutt et al., *The Standard of Evidence Required for Premarket Approval Under the Medical Device Amendments of 1976*, 47 FOOD & DRUG L.J. 605, 618–21 (1992). *But cf.* Final Report of the FDA Comm. for Clinical Review, *in* Subcomm. on Oversight & Investigations of the House Comm. on Energy & Commerce, *Less Than the Sum of Its Parts: Reforms Needed in the Organization, Management, and Resources of the FDA's Center for Devices and Radiological Health*, 103d Cong., at 105 (Comm. Print 1993) ("The fundamental principles underlying evaluation of any therapeutic intervention...are the same."); Philip J. Hilts, *FDA to Toughen Testing of Devices*, N.Y. TIMES, Mar. 5, 1993, at A18.

74. *See* Ron Winslow, *Study Meets Opposition from Doctors Who Use Laser Heart-Treatment Devices*, WALL ST. J., Oct. 30, 2000, at B10.

75. *See* Benjamin Freedman et al., *Placebo Orthodoxy in Clinical Research II: Ethical, Legal, and Regulatory Myths*, 24 J.L. MED. & ETHICS 252 (1996); Samuel Hellman & Deborah S. Hellman, *Of Mice but Not Men: Problems of the Randomized Clinical Trial*, 324 NEW ENG. J. MED. 1585 (1991); Kenneth J. Rothman & Karin B. Michels, *The Continuing Unethical Use of Placebo Controls*, 331 NEW ENG. J. MED. 394, 397 (1994); C. Michael Stein & Theodore Pincus, *Placebo-Controlled Studies in Rheumatoid Arthritis: Ethical Issues*, 353 LANCET 400 (1999); Susan Okie, *Health Officials Debate Ethics of Placebo Use*, WASH. POST, Nov. 24, 2000, at A3 (explaining that a recent revision to the Declaration of Helsinki prohibiting most uses of placebo controls sparked this latest debate). Aside from ethical objections, some commentators argue that placebo-controlled trials, which merely attempt to establish that the investigational treatment is "better than nothing," facilitate the approval of expensive new products that offer little or no advantage over existing treatments. *See* Freedman et al., *supra*, at 255–56, 258.

patient outcomes in any event.[76] Nonetheless, biomedical researchers contend that placebo-controlled trials provide the best method for judging efficacy,[77] especially for highly variable and subjective conditions such as depression or pain.[78] Whatever the merits of these competing arguments,[79] no one really doubts the value of RCTs (placebo-controlled or otherwise) in producing useful data about therapeutic interventions, but a variety of ethical and practical constraints make them exceedingly difficult to undertake.

III. UNTANGLING THE SOURCES OF INFORMATION

EBM urges physicians to invert their normal reliance on anecdotal experience and look instead for evidence from RCTs or, in the absence of such research, observational studies. Although some commentators have argued that outcomes research may provide more meaningful guidance than an RCT about the effectiveness of a medical treatment under real world conditions,[80] the hierarchy of

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76. *See* David Brown, *Medical Research Group Revises Guidelines on Placebos*, WASH. POST, Oct. 8, 2000, at A2; Okie, *supra* note 75, at A3 ("There is widespread consensus in the research community that using placebos is unethical whenever withholding an effective treatment would place study participants at risk of death or lasting disability. Certain kinds of medicines, such as antibiotics, cancer chemotherapy drugs and medicines to treat diabetes, are rarely tested against placebos."). The FDA has concurred with this position. *See* 53 Fed. Reg. 41,516, 41,519–20 (Oct. 21, 1988) ("[W]here no therapy has been shown to be effective [in treating a serious or life-threatening disease], it is scientifically and ethically appropriate to randomize patients to test drug and placebo.").

77. *See The Use of Placebo Controls in Clinical Trials*, Op. Am. Med. Ass'n Council on Ethical & Judicial Aff. No. E-2.075 (1996) ("Placebo controls are an important part of medicine's commitment to ensuring that the safety and efficacy of new drugs are sufficiently established."); Pamela I. Clark & Paul E. Leaverton, *Scientific and Ethical Issues in the Use of Placebo Controls in Clinical Trials*, 15 ANN. REV. PUB. HEALTH 19, 26–30 (1994); Joe Collier, Editorial, *Confusion over Use of Placebos in Clinical Trials*, 311 BRIT. MED. J. 821, 821–22 (1995). In supervising clinical trials for investigational drugs and devices, the FDA demands that sponsors design protocols to ensure the acquisition of usable knowledge. *See* 21 C.F.R. §§ 56.111(a)(2), 312.22(a) (2001).

78. *See* David P. Byar et al., *Design Considerations for AIDS Trials*, 323 NEW ENG. J. MED. 1343, 1345 (1990) ("Blinding is especially desirable when subjective end points, such as pain, functional status, or quality of life, are studied, because such evaluations are open to substantial bias."); Asbjørn Hróbjartsson & Peter C. Gøtzsche, *Is the Placebo Powerless? An Analysis of Clinical Trials Comparing Placebo with No Treatment*, 344 NEW ENG. J. MED. 1594, 1599 (2001); Judith A. Turner et al., *The Importance of Placebo Effects in Pain Treatment and Research*, 271 JAMA 1609, 1612–13 (1994).

79. *See generally* Sharona Hoffman, *The Use of Placebos in Clinical Trials: Responsible Research or Unethical Practice?*, 33 CONN. L. REV. 449 (2001); Timothy S. Jost, *The Globalization of Health Law: The Case of Permissibility of Placebo-Based Research*, 26 AM. J.L. & MED. 175 (2000).

80. *See* John Concato et al., *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 NEW ENG. J. MED. 1887, 1890–92 (2000); Alvan R. Feinstein & Ralph I. Horowitz, *Problems in the "Evidence" of "Evidence-Based Medicine,"* 103 AM. J. MED. 529 (1997); Andre Knottnerus & Geert Jan Dinant, Editorial, *Medicine-Based Evidence, a Prerequisite for Evidence-Based Medicine*, 315

evidence is generally unassailable. At least two difficulties remain for physicians interested in practicing EBM: they must locate the evidence, and then they must make sense of it. Although statistically significant results from a methodologically sound RCT should trump the results of even a properly conducted observational study, how can a busy physician with no training in biostatistics critically appraise the relative quality of these two broad types of evidence,[81] much less distinguish between more closely comparable subcategories of research? Proponents of EBM offer various suggestions and short-cuts to help with these challenges.[82]

Practice patterns evolve in an essentially ad hoc fashion, reflecting the largely informal and unregulated flow of biomedical information.[83] As one set of commentators described the process:

> [S]tandards develop in a complicated way involving the interaction of leaders of the [medical] profession, professional journals and meetings, and networks of colleagues. Neither the Food and Drug Administration, the National Institutes of Health, the Department of Health and Human Services, nor state licensing boards have had much to do with shaping medical practice. Most clinical policies

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BRIT. MED. J. 1109 (1997); *see also* Nick Black, *Why We Need Observational Studies to Evaluate the Effectiveness of Health Care*, 312 BRIT. MED. J. 1215 (1996) (arguing that these research methods can complement one another); Ioannidis et al., *supra* note 64, at 829.

81. *See* John Geddes, *Evidence-Based Mental Health*, *in* EVIDENCE-BASED PRACTICE: A CRITICAL APPRAISAL 66, 81–82 (Liz Trinder & Shirley Reynolds eds., 2000) (describing the difficulties in interpreting studies of variable quality).

82. *See* RICHARD GROSS, DECISIONS AND EVIDENCE IN MEDICAL PRACTICE 31–33 (2001); DAVID L. SACKETT ET AL., EVIDENCE-BASED MEDICINE: HOW TO PRACTICE AND HOW TO TEACH EBM (2d ed. 2000); Brian Haynes & Andrew Haines, *Barriers and Bridges to Evidence-Based Clinical Practice*, 317 BRIT. MED. J. 273 (1998); Allen F. Shaughnessy et al., *Becoming an Information Master: A Guidebook to the Medical Information Jungle*, 39 J. FAM. PRAC. 489, 490–95 (1994). For instance, EBM has spawned its own journal that, like other "current awareness" sources, presents summaries of the latest useful research. *See Purpose and Procedure*, 4 EVIDENCE-BASED MED. 130, 130 (1999) (explaining that the journal is designed "to alert clinicians to important advances...by selecting from the biomedical literature those original and review articles whose results are most likely to be both true and useful"); *see also* Gordon H. Guyatt et al., Editorial, *Practitioners of Evidence-Based Care*, 320 BRIT. MED. J. 954, 955 (2000) (recognizing that time constraints make compilations of the original literature critical to implementation of EBM).

83. *See* Armin D. Weinberg et al., *Informal Advice- and Information-Seeking Between Physicians*, 56 J. MED. EDUC. 174, 175, 180 (1981); *see also* Jur Strobos, *Stoning a Dead Bird: Advertising Limits on Approved New Drugs*, 50 FOOD & DRUG L.J. 533, 536 (1995) (referring to an "underground information marketplace" for physicians that includes meetings and newspaper articles summarizing new research); *id.* at 540 (questioning the desirability of "the present system [of] underground information transfer" for clinical decisionmaking where "information is inconsistently disseminated by the academic community or through anonymous forms of communication"). *See generally* DIANA CRANE, INVISIBLE COLLEGES: DIFFUSION OF KNOWLEDGE IN SCIENTIFIC COMMUNITIES (1972).

> derive from a flow of reports in the literature, at meetings, and in peer discussions.[84]

Traditionally, physicians would look to trusted colleagues and local opinion leaders for guidance.[85] In some health care settings, opportunities for informal communications have been institutionalized. For instance, hospitals may sponsor "grand rounds" or "morbidity and mortality" conferences on a weekly basis as part of an internal quality assurance and continuing education program.[86]

The haphazard diffusion of new knowledge may result in one of two types of inappropriate responses.[87] In some cases, physicians may embrace new

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84. BARRY R. FURROW ET AL., HEALTH LAW: CASES, MATERIALS AND PROBLEMS 39–40 (4th ed. 2001); *see also* INSTITUTE OF MEDICINE, ASSESSING MEDICAL TECHNOLOGIES 9 (1985) ("The connection between favorable assessment of a technology and its subsequent diffusion into practice is a wandering path among clinicians, educators, researchers, professional bodies, journal editors, hospitals, drug and device manufacturers, third party payers, regulatory agencies, and others. Their various perspectives obscure responsibility for the diffusion of technologies."); David M. Eddy, *Clinical Policies and the Quality of Clinical Practice*, 307 NEW ENG. J. MED. 343, 343 (1982) (explaining that standards may evolve out of a range of communications, from "comments at meetings and grand rounds to conversations in x-ray reading rooms and hospital cafeterias"); David M. Eddy, *Practice Policies: Where Do They Come From?*, 263 JAMA 1265, 1265 (1990); Marshall B. Kapp, *'Cookbook" Medicine: A Legal Perspective*, 150 ARCHIVES INTERNAL MED. 496, 496 (1990) ("[S]tandards have come from sources ranging from physician lounge discussions to reports in the literature and at professional conferences to personal trial-and-error to the sales pitches of drug detail people.").

85. *See* U.S. OFFICE OF TECH. ASSESSMENT, STRATEGIES FOR MEDICAL TECHNOLOGY ASSESSMENT 73 (1982) (referring to "trend setters"); David Orentlicher, *The Influence of a Professional Organization on Physician Behavior*, 57 ALB. L. REV. 583, 602–03 (1994) (discussing role of local "opinion leaders" in altering practice patterns) (citing JAMES S. COLEMAN ET AL., MEDICAL INNOVATION: A DIFFUSION STUDY 79–112 (1966)); Stephen B. Soumerai et al., *Effect of Local Medical Opinion Leaders on Quality of Care for Acute Myocardial Infarction: A Randomized Controlled Trial*, 279 JAMA 1358, 1358 (1998); *see also* Greer, *supra* note 45, at 6, 23 ("[L]ocal life reinforces local 'knowledge.' Associations, interests, and habits require and elicit continuity of behavior."); Ann Lennarson Greer, Editorial, *The Two Cultures of Biomedicine: Can There Be a Consensus?*, 258 JAMA 2739, 2740 (1987) ("Only rare individuals will prefer outside information and communications to the consensus of trusted associates."). *See generally* EVERETT M. ROGERS, DIFFUSION OF INNOVATIONS (4th ed. 1995).

86. *See* John D. Stobo & Patrick A. Murphy, Editorial, *Medical Grand Rounds at Hopkins*, 261 JAMA 3164 (1989); *see also* Scott B. Markow, Note, *Penetrating the Walls of Drug-Resistant Bacteria: A Statutory Prescription to Combat Antibiotic Misuse*, 87 GEO. L.J. 531, 536–37 (1998) (describing the success of hospital-based educational efforts); *cf.* Stanley L. Pestotnik et al., *Implementing Antibiotic Practice Guidelines Through Computer-Assisted Clinical Support*, 124 ANNALS INTERNAL MED. 884, 888–89 (1996).

87. *See* Glenn Laffel & Donald M. Berwick, *Quality in Health Care*, 268 JAMA 407, 407 (1992) ("The connection between generating new knowledge in medical research and putting that knowledge to use in medical practice is remarkably tenuous."); Shirley Reynolds, *The Anatomy of Evidence-Based Practice: Principles and Methods*, *in* EVIDENCE-BASED PRACTICE, *supra* note 81, at 17, 19 ("The practical effect of this gap between research and professional practice is that dangerous or useless procedures continue

procedures and technologies prematurely, before much evidence exists to support their enthusiasm.[88] Of course, where no alternative treatments exist, such a decision may make perfect sense. Nonetheless, new modalities do not always represent improvements over old therapies, and physicians may fail to alter their preferences when evidence emerges that casts doubts on the newer treatment. In other situations, tremendous lag times may arise. A recent report by the Institute of Medicine noted that fifteen to twenty years may elapse before providers adopt effective new medical technologies.[89] Of course, apart from external (especially cost) constraints, there may be good reasons for not rushing to try the latest therapeutic innovation given the fact that initial clinical trials may fail to disclose delayed or infrequent side effects.[90] The ideal response to medical innovation lies somewhere between these two contradictory impulses.

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to be implemented, and that effective, safe procedures are often introduced slowly into clinical practice, if at all."); Jeoffrey K. Stross & William R. Harlan, *The Dissemination of New Medical Information*, 241 JAMA 2622, 2624 (1979). *See generally* NATIONAL COOPERATIVE HIGHWAY RESEARCH PROGRAM, GETTING RESEARCH FINDINGS INTO PRACTICE (Andrew Haines & Anna Donald eds., 1998).

88. *See* John F. Burnum, *Medical Practice A La Mode: How Medical Fashions Determine Medical Care*, 317 NEW ENG. J. MED. 1220 (1987); David A. Grimes, *Technology Follies: The Uncritical Acceptance of Medical Innovation*, 269 JAMA 3030, 3031–32 (1993); John McKinlay, *From "Promising Report" to "Standard Procedure": Seven Stages in the Career of a Medical Innovation*, 59 MILBANK Q. 374 (1981); Lincoln E. Moses & Byron Wm. Brown, Jr., *Experiences with Evaluating the Safety and Efficacy of Medical Technologies*, 5 ANN. REV. PUB. HEALTH 267, 288 (1984) ("Surgery provides many examples of procedures that have found broad acceptance before reliable evaluation and then been rejected later for inefficacy or other problems."); Abigail Zuger, *New Way of Doctoring: By the Book*, N.Y. TIMES, Dec. 16, 1997, at B11.

89. *See* INSTITUTE OF MEDICINE, CROSSING THE QUALITY CHASM: A NEW HEALTH SYSTEM FOR THE 21ST CENTURY 145 (2001); *see also* A. Haines & R. James, *Implementing Findings of Research*, 308 BRIT. MED. J. 1488, 1488 (1994) ("The medical literature is littered with examples of research findings that have not found timely acceptance in practice...."); Mark Sudlow et al., *Population-Based Study of Use of Anticoagulants Among Patients with Atrial Fibrillation in the Community*, 314 BRIT. MED. J. 1529 (1997) (concluding that warfarin is underutilized); Rita Rubin, *IUDs Rarely Used Because of Doctors' Perceptions, Study Says*, USA TODAY, Jan. 31, 2002, at 11D; Laurie Tarkan, *Absence of Urgency: A Deadly Problem When Strokes Occur*, N.Y. TIMES, Feb. 13, 2001, at D7 (reporting that the FDA's 1996 approval of tissue plasminogen activator (tPA) "was expected to revolutionize the way stroke patients were treated," but that, almost five years later, "[o]nly 2 percent to 3 percent of stroke patients actually receive the new drug, whereas 30 percent to 40 percent could benefit from it"). "In part, it is because creating a change in attitude among doctors [about the effectiveness of any treatment for stroke] is often a slow process." *Id.*

90. *See* Einer Elhauge, *The Limited Regulatory Potential of Medical Technology Assessment*, 82 VA. L. REV. 1525, 1547 n.49 (1996) ("Professional practice thus appropriately embodies some inertia against change."); Rochelle Sharpe, *MedWatch System Comes Under Fire: FDA Defends Drug Monitoring as Physicians, Advocates Are Cautious*, WALL ST. J., June 24, 1998, at B5; *see also* Tanenbaum, *supra* note 45, at 38 (finding that physicians express cynicism about the motivations of investigators and sponsors of efficacy studies).

In order to elicit an appropriate reaction to new information, someone must translate basic biomedical research into meaningful and accessible forms. As explained in the sections that follow, the results of observational studies and RCTs may reach physicians through publication in peer-reviewed medical journals, presentations at CME conferences, alerts issued by government agencies, and promotional materials distributed by suppliers of medical technologies. In addition, researchers may assemble this primary research in various ways and publish their summaries in journals or textbooks. Finally, by combining the available primary and secondary research with the judgment of experts, professional organizations now issue treatment recommendations in the form of clinical practice guidelines, which themselves get disseminated through more or less effective channels. All of these sources of relevant information compete for the attention of physicians, who face daunting challenges in navigating among them. Apart from its sheer volume and complexity, physicians must remain vigilant about the conflicts of interest that now permeate the biomedical literature.

A. Primary Research

As the editors of the *Journal of the American Medical Association* recently explained: "Publication of clinically important and relevant articles is necessary to help keep physicians and researchers informed about advances in medical science and, more important, to enable clinicians to provide the most scientifically based, up-to-date care for their patients."[91] Even a Chief Justice of the United States Supreme Court once extolled the virtues of medical journals:

> Their purpose is to assemble and disseminate to the profession relevant information bearing on patient care. The enormous expansion of medical knowledge makes it difficult for a general practitioner–or even a specialist–to keep fully current with the latest developments without such aids. In a sense these journals provide continuing education for physicians....[92]

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91. Phil B. Fontanarosa et al., Editorial, *Thanking Authors, Peer Reviewers, and Readers—Constancy in a Time of Change*, 283 JAMA 2016, 2017 (2000); *see also* Eugene Garfield, *Which Medical Journals Have the Greatest Impact?*, 105 ANNALS INTERNAL MED. 313 (1986); Gervasio A. Lamas et al., *Do the Results of Randomized Clinical Trials of Cardiovascular Drugs Influence Medical Practice?*, 327 NEW ENG. J. MED. 241, 247 (1992) (concluding that "well-executed, clinically relevant randomized trials published in highly visible clinical journals can have a measurable and prompt effect on patterns of medical practice"); George D. Lundberg et al., *Policy of AMA Journals Regarding Release of Information to the Public*, 265 JAMA 400, 400 (1991) (noting that "physicians rely on journal publication to provide full information they can assess").

92. United States v. Am. Coll. of Physicians, 475 U.S. 834, 850 (1986) (Burger, C.J., concurring) (rejecting, however, a medical association's claim for a tax exemption of its journal advertising revenues). In 1956, Congress established the National Library of Medicine (NLM) to "aid the dissemination and exchange" of biomedical information. *See* The Public Health and Welfare Act, Pub. L. No. 84-941, 70 Stat. 960 (1956) (codified as amended at 42 U.S.C. § 286(a) (2000)).

Physicians report that continuing medical education (CME) programs and medical journals have the most significant influence on their practice,[93] though research suggests that CME events have at best only a marginal impact.[94] Physicians do rely on the biomedical literature for the latest findings,[95] though in some instances they may become aware of new research only indirectly through media reports,[96] and they also may have unjustified confidence in the reliability of what they read.[97] Biomedical journals often include informal communications such

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93. *See* PAUL C. WEILER ET AL., A MEASURE OF MALPRACTICE: MEDICAL INJURY, MALPRACTICE LITIGATION, AND PATIENT COMPENSATION 128 tbl.6.3 (1993); E. Ray Stinson & Dorothy A. Mueller, *Survey of Health Professionals' Information Habits and Needs*, 243 JAMA 140, 140 (1980).

94. *See* Dave Davis et al., *Impact of Formal Continuing Medical Education: Do Conferences, Workshops, Rounds, and Other Traditional Continuing Education Activities Change Physician Behavior or Health Care Outcomes?*, 282 JAMA 867, 867 (1999) (concluding that traditional CME programs "do not appear to be effective in changing physician performance"); *see also id.* at 873 ("Knowledge is clearly necessary but not in and of itself sufficient to bring about change in physician behavior and patient outcomes."); David A. Davis et al., *Changing Physician Performance: A Systematic Review of the Effect of Continuing Medical Education Strategies*, 274 JAMA 700, 703 (1995) (finding that other forms of CME are more effective); David A. Davis et al., *Evidence for the Effectiveness of CME: A Review of 50 Randomized Controlled Trials*, 268 JAMA 1111, 1115 (1992); Phil R. Manning & Donald W. Petit, *The Past, Present, and Future of Continuing Medical Education*, 258 JAMA 3542, 3543–44 (1987); Andrew D. Oxman et al., *No Magic Bullets: A Systematic Review of 102 Trials of Interventions to Improve Professional Practice*, 153 CAN. MED. ASS'N J. 1423 (1995); Zuger, *supra* note 43, at D5 ("Dozens of studies have tried and failed to show that listening to a [CME] talk and even passing a test afterward have the slightest effect on the way a doctor has, say, treated diabetes for the last 30 years.").

95. *See* Milton Liebman & Robert L. Kennett, *Too Tight a Focus in Micromarketing?*, MED. MKTG. & MEDIA, July 1994, at 66 (reporting that sixty-nine percent of physicians surveyed identified medical journals as their most important source of information); Jeoffrey K. Stross & William R. Harlan, *The Dissemination of Relevant Information on Hypertension*, 246 JAMA 360, 362 (1981).

96. *See* Pia Pini, *Media Wars: Medicine in the Media*, 346 LANCET 1681, 1682 (1995); Robert Steinbrook & Bernard Lo, *Informing Physicians About Promising New Treatments for Severe Illnesses*, 263 JAMA 2078, 2080 (1990); Howard Kurtz, *Embargo Dispute Highlights Scientific Journals' Influence on News*, WASH. POST, June 16, 1991, at A10; Ellen Ruppel Shell, *The Hippocratic Wars*, N.Y. TIMES MAG., June 28, 1998, at 34 (explaining that editors of major biomedical journals increasingly court the lay media, and noting that "doctors have no more than three hours a week to read the latest journals, and there are nearly 4,000 of them competing for a physician's attention," but cautioning that press reports of the latest research findings are "prone to misinterpretation by physicians as well as by the public"); *see also* Ray Moynihan et al., *Coverage by the News Media of the Benefits and Risks of Medications*, 342 NEW ENG. J. MED. 1645, 1647–49 (2000) (finding that reports in the lay media describing new pharmaceutical research often provided incomplete information).

97. *See* R. Brian Haynes, *Loose Connections Between Peer-Reviewed Clinical Journals and Clinical Practice*, 113 ANNALS INTERNAL MED. 724, 725 (1990) ("[T]he high concentration of preliminary studies undoubtedly contributes to the premature adoption of clinical innovations....Many physicians rely on the peer review process to determine the

as letters to the editor or case histories; these may provide preliminary information that is later confirmed by epidemiological studies or clinical trials,[98] but the fact of publication does not make these sorts of anecdotal reports particularly significant.[99] The sections that follow focus on some of the limitations in published reports describing primary biomedical research.

1. Problems with Editorial Peer Review

As in other scientific disciplines, editorial peer review has long served an important quality control function in biomedical publications.[100] It has a number of shortcomings, however, that may limit its utility as a mechanism for validating the information that appears in print.[101] Peer review in the publication process cannot guarantee the accuracy or validity of the reported research. Authors may make statistically suspect claims,[102] and they often fail to provide valuable context such

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validity of such claims and thus can be easily misled."); Jack P. Lipton & Alan M. Hershaft, *On the Widespread Acceptance of Dubious Medical Findings*, 26 J. HEALTH & SOC. BEHAV. 336, 344 (1985) ("The conceptual and methodological problems that we have uncovered are in themselves alarming but even more so are the erroneous citations and the general acceptance of these findings by the medical profession.").

98. *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, *supra* note 31, at 474–75; Ross J. Simpson, Jr. & Thomas R. Griggs, *Case Reports and Medical Progress*, 28 PERSP. IN BIO. & MED. 402, 403–04 (1985).

99. *See* Arthur S. Relman, Editorial, *How Reliable Are Letters?*, 308 NEW ENG. J. MED. 1219, 1220 (1983) ("There is a risk that uncritical readers may be misled if they fail to appreciate the tentative and incomplete nature of the evidence contained in these letters.").

100. *See generally* MEDICAL JOURNALS AND MEDICAL KNOWLEDGE (W.F. Bynum et al. eds., 1992); Franz J. Ingelfinger, *Peer Review in Biomedical Publication*, 56 AM. J. MED. 686 (1974).

101. *See* Paul Cotton, *Flaws Documented, Reforms Debated at Congress on Journal Peer Review*, 270 JAMA 2775, 2775 (1993) ("Research is revealing much room for improvement in the long-concealed world of medical journal peer review."); Joan Stephenson, *Medical Journals Turn Gaze Inward to Examine Process of Peer Review*, 278 JAMA 1389 (1997); Ann C. Weller, *Editorial Peer Review in US Medical Journals*, 263 JAMA 1344 (1990); *see also* Lars Noah, *Sanctifying Scientific Peer Review: Publication as a Proxy for Regulatory Decisionmaking*, 59 U. PITT. L. REV. 677, 695–709 (1998) (cataloging limitations).

102. *See* John W. Williamson et al., *The Quality of Medical Literature: An Analysis of Validation Assessments*, *in* MEDICAL USES OF STATISTICS 370, 383 (John C. Bailar III & Frederick Mosteller eds., 1986) ("[T]he average practitioner will find relatively few journal articles that are scientifically sound in terms of reporting usable data and providing even moderately strong support for their inferences....The mere fact that research reports are published, even in the most prestigious journals, is no guarantee of their quality."); Rachel Nowak, *Problems in Clinical Trials Go Far Beyond Misconduct*, 264 SCIENCE 1538, 1539–40 (1994); Stuart J. Pocock et al., *Statistical Problems in the Reporting of Clinical Trials: A Survey of Three Medical Journals*, 317 NEW ENG. J. MED. 426, 431–32 (1987) (finding that reports of comparative clinical trials tend to exaggerate treatment differences); John M. Yancey, Editorial, *Ten Rules for Reading Clinical Research Reports*, 159 AM. J. SURGERY 533, 534 (1990) ("Most of the errors [found in the medical

as information about toxicity identified during clinical trials of a therapy's efficacy.[103] In addition, consistent with the predictions of cognitive psychology, physicians appear to respond more favorably to research that describes relative rather than absolute therapeutic gains.[104] A study reporting that an experimental treatment doubles a patient's chances of survival sounds better than a study reporting that the treatment increases a patient's chances of survival from two to four percent.

Although published articles carry the imprimatur of originality and plausibility, referees and editors cannot catch subtle methodological errors much less authenticate the underlying research. Efforts at replication, refinement, or cross-checking may reveal limitations in the original study's conclusions or, worse yet, suggest their invalidity. Even more seriously, subsequent investigation may identify outright fabrication of the data reported in studies after they have been published in a peer-reviewed journal. During the last few decades, several instances of misconduct have come to light,[105] and the publication of falsified research can jeopardize the public health.[106] Editorial peer review cannot ferret out

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literature] are of the magnitude of claiming to have scientific evidence that one surgical procedure is superior to another when no such valid scientific data are presented.").

103. *See* John P.A. Ioannidis & Joseph Lau, *Completeness of Safety Reporting in Randomized Trials*, 285 JAMA 437, 442 (2001) ("[S]afety reporting is often inadequate and neglected. Key information that would take minimal space to report is often missing."); Tom Pelton, *Medical Experiment Disclosure Hinges on a Flawed Honor System*, BALT. SUN, Aug. 12, 2001, at 1A.

104. *See* Marco Bobbio et al., *Completeness of Reporting Trial Results: Effect on Physicians' Willingness to Prescribe*, 343 LANCET 1209, 1210–11 (1994); H.C. Bucher et al., *Influence of Method of Reporting Study Results on Decision of Physicians to Prescribe Drugs to Lower Cholesterol Concentration*, 309 BRIT. MED. J. 761, 763 (1994); C. David Naylor et al., *Measured Enthusiasm: Does the Method of Reporting Trial Results Alter Perceptions of Therapeutic Effectiveness?*, 117 ANNALS INTERNAL MED. 916, 918–20 (1992).

105. *See* WILLIAM BROAD & NICHOLAS WADE, BETRAYERS OF THE TRUTH 87 (1982) (estimating that "every major case of fraud that becomes public is the representative of some 100,000 others, major and minor combined, that lie concealed in the marshy wastes of the scientific literature"); *see also* United States v. Keplinger, 776 F.2d 678, 684–90 (7th Cir. 1985) (affirming fraud convictions of toxicologists who generated false product safety data submitted to the FDA); Lawrence K. Altman, *Researcher Falsified Data in Breast Cancer Study*, N.Y. TIMES, Mar. 14, 1994, at A1 (describing errors in a study discovered several years after its publication in the *New England Journal of Medicine*).

106. *See* House Comm. on Government Operations, *Are Scientific Misconduct and Conflicts of Interest Hazardous to Our Health?*, H.R. REP. NO. 101-688, at 65 (1990) ("When scientific misconduct and conflicts of interest result in research publications that misrepresent the safety or effectiveness of drugs, the public is misled and sometimes endangered."); Michael J.G. Farthing, *An Editor's Response to Fraudsters*, 316 BRIT. J. MED. 1729, 1730 (1998); Larry Norton, Editorial, *High-Dose Chemotherapy for Breast Cancer: "How Do You Know?,"* 19 J. CLINICAL ONCOLOGY 2769, 2769 (2001) (explaining that the widespread publication of a fraudulent study on a controversial new treatment for advanced breast cancer "influenced major thinkers in this field and may have put patients in danger").

scientific fraud of this sort.[107] Occasionally, subsequent research leads an author to publish a qualification or retraction of his or her article,[108] or, where serious but unresolved questions are raised about an article, editors have withdrawn their journal's sanction from the article.[109] The danger is that physicians may not always become aware of this subsequent history.[110]

Although most major scientific journals utilize referees, levels of rigor differ substantially.[111] Referees provide only fairly superficial assessments of the manuscripts that they receive. Studies of the process sometimes find a substantial portion of accepted manuscripts would have been rejected by a different set of referees.[112] At best, editorial peer review manages to filter out obviously sloppy work, though persistent authors eventually manage to find an outlet for publication

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107. *See* Drummond Rennie, Editorial, *Editors and Auditors*, 261 JAMA 2543, 2544 (1989) ("[A]lthough it may work well when the questions being asked of it are the questions of science, peer review has proved to be of little use in determining if the information provided in the first place is either complete or honest."); Drummond Rennie, Editorial, *More Peering into Editorial Peer Review*, 270 JAMA 2856, 2857 (1993) ("Fraud by an author is almost impossible for reviewers and editors to detect and readers do not do so, while duplicate publication remains common.").

108. *See* Gwendolyn L. Snodgrass & Mark P. Pfeifer, *The Characteristics of Medical Retraction Notices*, 80 BULL. MED. LIBR. ASS'N 328, 328 (1992) ("During the past twenty years, the publications of letters, announcements, and editorials retracting previously published papers has become a relatively common event in the medical journal literature.").

109. *See* Paul J. Friedman, *Correcting the Literature Following Fraudulent Publication*, 263 JAMA 1416, 1419 (1990); Richard Horton, *Revising the Research Record*, 346 LANCET 1610, 1611 (1995).

110. *See* John M. Budd et al., *Phenomena of Retraction: Reasons for Retraction and Citations to the Publications*, 280 JAMA 296, 296 (1998) ("[T]he biomedical literature is also affected by error that can render the reported results of research useless at best and dangerous at worst."); Mark P. Pfeifer & Gwendolyn L. Snodgrass, *The Continued Use of Retracted, Invalid Scientific Literature*, 263 JAMA 1420, 1422 (1990). The National Library of Medicine now includes "Retraction of Publication" as a separate subject matter entry in its indices, and its electronic databases include matched tags to indicate when a retrieved article has been retracted. *See* Sheldon Kotzin & Peri L. Schuyler, *NLM's Practices for Handling Errata and Retractions*, 77 BULL. MED. LIBR. ASS'N 337, 338 (1989).

111. *See* John C. Burnham, *The Evolution of Editorial Peer Review*, 263 JAMA 1323 (1990); Lowell L. Hargens, *Variations in Journal Peer Review Systems: Possible Causes and Consequences*, 263 JAMA 1348 (1990); Ann C. Weller, *Editorial Peer Review in US Medical Journals*, 263 JAMA 1344, 1347 (1990); *see also* Jonathan D. Eldredge, *Identifying Peer-Reviewed Journals in Clinical Medicine*, 85 BULL. MED. LIBR. ASS'N 418, 421 (1997) ("Confusion about the identities of peer-reviewed journals in clinical medicine continue to persist. Practices at journals that describe themselves as 'peer-reviewed' vary widely.").

112. *See* SHEILA JASANOFF, THE FIFTH BRANCH: SCIENCE ADVISERS AS POLICYMAKERS 69–70 (1990); *see also* DARYL E. CHUBIN & EDWARD J. HACKETT, PEERLESS SCIENCE: PEER REVIEW AND U.S. SCIENCE POLICY 100 (1990) ("Fallibility of judgment alone, without appeal to bias or venality, can generate a significant number of mistaken judgments.").

of any research, no matter what its intrinsic merit.[113] In that case, however, rigorous editorial peer review by the more prominent medical journals may shunt lower quality work to obscure, archival publications that generally do not reach practicing physicians.

To the extent that referees and editors try to assess the originality and potential importance of a manuscript, a "publication bias" may work in favor of novel (and perhaps unreliable) results over the more mundane replication of prior work or research that happens to falsify an interesting hypothesis.[114] Indeed, some journals now offer a form of expedited peer review for manuscripts of significant clinical or public health importance, particularly those that report the results of large-scale RCTs.[115] Researchers may anticipate such real or perceived editorial preferences by not going to the effort of submitting their uninteresting results for publication. If it exists, such a publication bias may have important consequences for health care professionals who rely on the published literature for a balanced assessment of the relative safety and effectiveness of therapeutic interventions.[116]

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113. *See* STEPHEN LOCK, A DIFFICULT BALANCE: EDITORIAL PEER REVIEW IN MEDICINE 39–41, 85 (1985) (suggesting that editorial peer review channels manuscripts to lesser journals but prevents publication in only a small percentage of cases).

114. *See* Kay Dickersin, *The Existence of Publication Bias and Risk Factors for Its Occurrence*, 263 JAMA 1385, 1386–88 (1990); *see also* David L. Sackett, *Bias in Analytic Research*, 32 J. CHRONIC DISEASES 51, 61 (1979) ("Authors are more likely to submit, and editors accept, positive than null results....When a topic is hot, neither investigators nor editors may be able to resist the temptation to publish additional results, no matter how preliminary or shaky...."). Results that appear to debunk the conventional wisdom also may appeal to editors. *See* Paul J. Friedman, *Mistakes and Fraud in Medical Research*, 20 LAW MED. & HEALTH CARE 17, 20 (1992) ("Journals are more likely to publish work that effectively contradicts previous observations than papers which are supportive."); *see also* Marcia Angell, Editorial, *Negative Studies*, 321 NEW ENG. J. MED. 464 (1989); Robert Temple, *Commentary on "The Architecture of Government Regulation of Medical Products,"* 82 VA. L. REV. 1877, 1898–90 (1996) (describing published RCTs finding that off-label uses of drugs in cardiac patients not only failed to work but actually increased mortality); Susan Okie, *Trial of Antibiotics for Chronic Lyme Disease Halted*, WASH. POST, June 13, 2001, at A2 (reporting that a study forthcoming in the *New England Journal of Medicine* "casts doubt on some doctors' practice of treating people with chronic Lyme disease with antibiotics for months or years on the theory that microbes hiding in the body are responsible for the symptoms").

115. *See* Margaret A. Winker & Phil B. Fontanarosa, Editorial, *JAMA-EXPRESS: Rapid Peer Review and Publication*, 281 JAMA 1754, 1755 (1999); *see also* Jerome P. Kassirer & Marcia Angell, Editorial, *Prepublication Release of* Journal *Articles*, 337 NEW ENG. J. MED. 1762, 1763 (1997) ("[I]n the few instances in which a study suggests an immediate and important change in practice, we will continue to try to convey information to doctors and patients as quickly as possible....").

116. *See* Iain Chalmers, *Underreporting Research Is Scientific Misconduct*, 263 JAMA 1405, 1405–06 (1990) ("Failure to publish 'disappointing' or 'uninteresting' research results, or failure to report results in sufficient detail, may either lead patients to receive ineffective or dangerous forms of care or result in a delay in recognizing that other forms of care are beneficial."); Robert John Simes, *Publication Bias: The Case for an International Registry of Clinical Trials*, 4 J. CLINICAL ONCOLOGY 1529, 1538 (1986) (explaining that,

In addition, subsequent researchers may compound this publication bias by selective citation to published studies reporting positive results.[117] When authors later synthesize results in systematic reviews or meta-analyses,[118] they will have a skewed picture of the existing research based on what journal editors have decided to publish, and their resulting compilations will magnify this error.[119] Imagine that different researchers have undertaken five RCTs of a particular therapeutic intervention and that two of the studies find a statistically significant advantage to the treatment while the other three fail to do so—if one or more of the latter studies do not appear in print because of a publication bias,[120] a synthesis of the published research will provide exaggerated confidence in the therapeutic utility of the intervention under consideration.[121]

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because of the publication bias, "a traditional review of the published literature could result in overly optimistic conclusions concerning new therapies").

117. *See* Clarke & Chalmers, *supra* note 61, at 280 ("Studies that have yielded relatively dramatic results are more likely to be cited in reports of subsequent similar studies than previous studies yielding unremarkable point estimates of effects."); U. Ravnskov, *Cholesterol Lowering Trials in Coronary Heart Disease: Frequency of Citation and Outcome*, 305 BRIT. MED. J. 15, 18–19 (1992).

118. *See infra* Part III.B.

119. *See* Colin B. Begg & Jesse A. Berlin, *Publication Bias and Dissemination of Clinical Research*, 81 J. NAT'L CANCER INST. 107, 109 (1989); Drummond Rennie & Annette Flanagin, Editorial, *Publication Bias: The Triumph of Hope over Experience*, 267 JAMA 411, 411 (1992).

120. *See* Philippa J. Easterbrook et al., *Publication Bias in Clinical Research*, 337 LANCET 867, 870–71 (1991); Robert John Simes, *Confronting Publication Bias: A Cohort Design for Meta-Analysis*, 6 STAT. MED. 11, 11 (1987) ("Clinical trials which fail to show any treatment difference are less likely to be published owing to investigators not writing up the results or owing to journals declining to publish such 'uninteresting' information." (footnotes omitted)); Jerome M. Stern & R. John Simes, *Publication Bias: Evidence of Delayed Publication in a Cohort Study of Clinical Research Projects*, 315 BRIT. MED. J. 640, 644 (1997).

121. *See* Kay Dickersin et al., *Factors Influencing Publication of Research Results: Follow-up of Applications Submitted to Two Institutional Review Boards*, 267 JAMA 374, 378 (1992); Kay Dickersin et al., *Identifying Relevant Studies for Systematic Reviews*, 309 BRIT. MED. J. 1286, 1290 (1994); Richard Peto, *Why Do We Need Systematic Overviews of Randomized Trials?*, 6 STAT. MED. 233, 235 (1987); *see also* John P.A. Ioannidis, *Effect of the Statistical Significance of Results on the Time to Completion and Publication of Randomized Efficacy Trials*, 279 JAMA 281, 286 (1998) (concluding that "publication lag [for negative RCTs] may affect evidence-based medicine"); Alejandro R. Jadad & Drummond Rennie, *The Randomized Controlled Trial Gets a Middle-Aged Checkup*, 279 JAMA 319, 319–20 (1998) ("[I]f trials with positive results are published years faster than those with negative results, new interventions will be accepted as effective in the absence of evidence to the contrary, although the evidence may already have been gathered."); Robert Temple, *Meta-Analysis and Epidemiologic Studies in Drug Development and Postmarketing Surveillance*, 281 JAMA 841, 842 (1999) ("Aside from the recognized risk that publication bias may leave the meta-analysis with a biased sample of trials to combine, it is also possible that awareness of the major study results might stimulate the decision to perform a meta-analysis in one case but not another.").

Scientific conferences provide another important conduit for the dissemination of information about cutting-edge research, usually in the form of abstracts. Typically, these summaries describe only preliminary study results, and they may do so in ways that exaggerate the findings.[122] Even if subjected only to a cursory form of peer review and not formally published, these abstracts indirectly become part of the primary literature insofar as clinical researchers subsequently cite the results.[123] In addition, the abstract selection process appears to impact decisions by researchers about pursuing formal publication, so biases in favor of positive outcomes that are introduced at this stage may reinforce any later publication bias.[124]

2. Managing Information Overload

Even if peer review worked perfectly, practicing physicians would struggle to keep up with the volume of information produced, much less separate the wheat from the chaff. The amount of published biomedical literature has grown dramatically in the last few decades. Today, there are more than 25,000 biomedical journals worldwide,[125] which publish more than two million articles annually.[126] MEDLINE, an electronic database covering less than 4,000 of these journals, contains over nine million citations and adds more than 30,000 new

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122. *See* Friedman, *supra* note 114, at 21.

123. *See* Michael L. Callaham et al., *Positive-Outcome Bias and Other Limitations in the Outcome of Research Abstracts Submitted to a Scientific Meeting*, 280 JAMA 254, 256 (1998) ("Presentation of scientific studies at meetings is an important part of the dissemination of knowledge, but half of these studies appear only as abstracts and never undergo any other peer review..., yet abstracts are cited as often as fully published papers.").

124. *See id.* (finding a positive-outcome bias in the selection of abstracts); Roberta W. Scherer et al., *Full Publication of Results Initially Presented in Abstracts: A Meta-Analysis*, 272 JAMA 158, 161 (1994); *see also* Ellen J. Weber et al., *Unpublished Research from a Medical Specialty Meeting: Why Investigators Fail to Publish*, 280 JAMA 257, 259 (1998) ("Because failure to publish completed research affects medical practice, it is imperative that specialty societies understand the potential impact of their decisions and make additional efforts to encourage all investigators, not just those whose abstracts are accepted for presentation, to pursue full publication.").

125. *See* Lawrence K. Altman, *The Ingelfinger Rule, Embargoes, and Journal Peer Review—Part I*, 347 LANCET 1382 (1996); *see also* Stephen Lock, *Information Overload: Solution by Quality?*, 284 BRIT. MED. J. 1289 (1982); Byron H. Waksman, *Information Overload in Immunology: Possible Solutions to the Problem of Excessive Publication*, 124 J. IMMUNOLOGY 1009, 1009–12 (1980). *See generally* COPING WITH THE BIOMEDICAL LITERATURE: A PRIMER FOR THE SCIENTIST AND THE CLINICIAN (Kenneth S. Warren ed., 1981).

126. *See* Mulrow & Lohr, *supra* note 35, at 251; *see also* David T. Durack, *The Weight of Medical Knowledge*, 298 NEW ENG. J. MED. 773, 774 (1978) (reporting dramatic increases in the weight of *Index Medicus* over the course of the last century); Ronna Henry Siegel, Editorial, *Updates Linking Evidence and Experience*, 279 JAMA 1395, 1395 (1998) ("[T]he number of scientific articles has been estimated to double every 10 to 15 years.").

references each month.[127] Electronic databases certainly help physicians who may want to access this vast literature,[128] but the rapid availability of this wealth of information also may overwhelm clinicians when they struggle to make use of it.[129] In addition, abstracts of published articles, which may be all that one can access using MEDLINE or another electronic database, often contain significant omissions or errors.[130]

Social scientists have questioned the oft-voiced concern about "information overload" in the general population. When they make purchasing decisions, consumers may have difficulty either in acquiring all relevant

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127. *See* P. Robert Hubbs et al., Editorial, *Medical Information on the Internet*, 280 JAMA 1363, 1363 (1998); *see also* Eric Nagourney, *For Medical Journals, A New World Online*, N.Y. TIMES, Mar. 20, 2001, at D1 (explaining that another NIH archival project, PubMed, urges journals to make their full text available on the Internet). The World Health Organization has persuaded the publishers of nearly 1000 medical journals to provide free access to doctors in the Third World. *See* David Brown, *Free Access to Medical Journals to Be Given to Poor Nations*, WASH. POST, July 9, 2001, at A12 (adding that "the program may help to spread the 'evidence-based medicine' revolution").

128. *See* Fontanarosa, *supra* note 91, at 2016 (noting "the tremendous capabilities of electronic information dissemination, with the ever-increasing power, speed, reach, and convenience of the Internet," adding that this "has revolutionized and probably changed forever the dissemination of scientific information"); Guyatt et al., *supra* note 35, at 1295 ("[F]urther advances in easy electronic access to all levels of evidence-based resources should dramatically increase the feasibility of evidence-based practice in the next decade."); R. Brian Haynes et al., *Online Access to MEDLINE in Clinical Settings: A Study of Use and Usefulness*, 112 ANNALS INTERNAL MED. 78, 78 (1990); Dereck L. Hunt et al., *Users' Guides to the Medical Literature: XXI. Using Electronic Health Information Resources in Evidence-Based Practice*, 283 JAMA 1875, 1878–79 (2000); Donald A.B. Lindberg et al., *Use of MEDLINE by Physicians for Clinical Problem Solving*, 269 JAMA 3124, 3128–29 (1993); Robert Sikorski & Richard Peters, *Medical Literature Made Easy: Querying Databases on the Internet*, 277 JAMA 959 (1997); *see also* Milt Freudenheim, *Medical Web Sites Transforming Visits to Doctors*, N.Y. TIMES, May 30, 2000, at C1 ("[P]rimary care doctors say they appreciate the ability to get information online faster than they can by calling a colleague or opening a textbook that may be outdated.").

129. *See* Donald A.B. Lindberg & Betsy L. Humphreys, *Medicine and Health Care on the Internet: The Good, the Bad, and the Ugly*, 280 JAMA 1303, 1303–04 (1998); Rosoff, *supra* note 17, at 379 ("[N]ew knowledge is being generated in the medical world more rapidly than ever before. Ironically, the new forms of electronic communication, data gathering and analysis are as much responsible for this as is any change in the pace of traditional forms of medical research...."). The same phenomenon may affect practicing lawyers inundated by the wealth of more easily accessible information. *See* M. ETHAN KATSH, THE ELECTRONIC MEDIA AND THE TRANSFORMATION OF LAW 43–46, 201 (1989); Nazareth A. M. Pantaloni III, *Legal Databases, Legal Epistemology, and the Legal Order*, 86 LAW LIBR. J. 679, 698–705 (1994).

130. *See* Friedman, *supra* note 114, at 21; Roy M. Pitkin et al., *Accuracy of Data in Abstracts of Published Research Articles*, 281 JAMA 1110 (1999). For this reason and others, some commentators have recommended greater attention to the content and format of these summaries. *See* R. Brian Haynes et al., *More Informative Abstracts Revisited*, 113 ANNALS INTERNAL MED. 69, 69 (1990); Margaret A. Winker, Editorial, *The Need for Concrete Improvement in Abstract Quality*, 281 JAMA 1129, 1130 (1999).

information or in taking available information into account because of task complexity.[131] Consumers struggling under the constraints of "bounded rationality" may cope by "satisficing,"[132] which means that they settle for less than optimal choices because of the excessive costs involved in acquiring and assimilating all of the available information.[133]

Although physicians should have the training and expertise necessary to manage large quantities of complex information, the pace of knowledge production and acquisition presents significant challenges for the medical profession.[134] They have ethical and legal obligations to stay abreast of the latest research in their fields,[135] but increasingly time-strapped practitioners cannot

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131. *See* Baruch Fischhoff, *Cognitive Liabilities and Product Liability*, 1 J. PROD. LIAB. 207, 207–08 (1977) ("[P]eople have a great deal of difficulty making proper decisions under conditions of uncertainty,...in part because they lack the cognitive capacity for combining the large amounts of information often involved in making decisions."); *see also* W. KIP VISCUSI, REFORMING PRODUCTS LIABILITY 139–40 (1991) (summarizing research indicating that "individuals can seldom recall more than six pieces of information from a label"); John F. Kihlstrom, *The Cognitive Unconscious*, 237 SCIENCE 1445, 1447 (1987) ("It is a fundamental premise of cognitive psychology that the amount of attention that can be allocated to various activities is limited, producing a bottleneck in information processing."); *cf.* Fischhoff, *supra*, at 208 ("Although most research has focused upon the cognitive processes of lay people, there is reason to believe that many of these judgmental problems afflict experts, too, when they are forced to rely on their intuitions.").

132. *See* 3 HERBERT A. SIMON, MODELS OF BOUNDED RATIONALITY 295–98 (1997).

133. *See* James R. Bettman et al., *Constructive Consumer Choice Processes*, 25 J. CONSUMER RES. 187, 190 (1998); David M. Grether et al., *The Irrelevance of Information Overload: An Analysis of Search and Disclosure*, 59 S. CAL. L. REV. 277, 301 (1986) ("[T]he information overload idea–that too much information causes dysfunction–is a myth. Instead, when choice sets become large or choice tasks complex relative to consumers' time or skill, consumers satisfice rather than optimize."); Latin, *supra* note 19, at 1211–15; *see also* Ellen C. Garbarino & Julie A. Edell, *Cognitive Effort, Affect, and Choice*, 24 J. CONSUMER RES. 147, 148 (1997) ("[P]eople are willing to forego some benefits to conserve cognitive effort.").

134. *See* Jeff Goldsmith, *How Will the Internet Change Our Health System?*, HEALTH AFF., Jan.–Feb. 2000, at 148, 149 ("Health care providers and systems are staggeringly inefficient at assimilating and processing information and at converting that information to knowledge. Part of the problem is that the core knowledge base of health care, biomedical science, is expanding at a geometric rate...."); *see also id.* at 152 ("The decay rate of scientific knowledge that physicians acquire in the basic science portion of their medical education is scarily rapid."); Mark R. Chassin, *Is Health Care Ready for Six Sigma Quality?*, 76 MILBANK Q. 565, 574–76, 579 (1998) ("Physicians [today] face a far more complicated reality of constantly changing and increasing medical knowledge.").

135. *See* Am. Med. Ass'n, *Principles of Medical Ethics: Principle V*, *in* COUNCIL ON ETHICAL & JUDICIAL AFF., CODE OF MEDICAL ETHICS: CURRENT OPINIONS WITH ANNOTATIONS (1999) ("A physician shall continue to study, apply and advance scientific knowledge...."); *id.*, Opinion No. 9.08 (describing one "role of the physician" as "a student who constantly seeks to keep abreast of new medical knowledge"); *see also infra* note 411 (same duty in tort).

possibly hope to keep up.[136] In addition, health care professionals may find it difficult to evaluate the reliability of various types and sources of information.[137] Rapid progress in biomedical research provides one of the explanations for the growth in specialization by physicians,[138] which may improve their ability to absorb and critically appraise the new information, but it also risks increasing costs and fragmenting patient care.[139]

Undoubtedly, physicians also satisfice when they make diagnostic and therapeutic decisions in the face of uncertainty,[140] but the consequences of making

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136. *See* Timothy Stoltzfus Jost, *Oversight of the Quality of Medical Care: Regulation, Management, or the Market?*, 37 ARIZ. L. REV. 825, 843–44 (1995) ("No one physician can comprehend the totality of what is known; each must act based on his or her limited base of knowledge and experience."); Brett A. Kirkpatrick, *History of the Development of Medical Information*, 61 BULL. N.Y. ACAD. MED. 230, 236 (1985); John W. Williamson et al., *Health Science Information Management and Continuing Education of Physicians*, 110 ANNALS INTERNAL MED. 151, 158 (1989).

137. *See* David M. Eddy, *Anatomy of a Decision*, 263 JAMA 441, 443 (1990) ("A physician who is trained to do surgery or read a CT scan can no more be expected to research scores of articles, analyze experimental designs, adjust for biases, and perform calculations, than a statistician can be expected to remove an appendix."); William L. Roper et al., *Effectiveness in Health Care: An Initiative to Evaluate and Improve Medical Practice*, 319 NEW ENG. J. MED. 1197, 1197 (1988) ("Research on medical interventions is often poorly designed and methodologically flawed. Many physicians lack the skills to interpret and critically evaluate medical literature...."); Liz Trinder, *Introduction: The Context of Evidence-Based Practice*, *in* EVIDENCE-BASED PRACTICE, *supra* note 81, at 1, 4.

138. *See* Jeremiah A. Barondess, Editorial, *Specialization and the Physician Workforce: Drivers and Determinants*, 284 JAMA 1299, 1300 (2000) (suggesting that "the burst of new knowledge flowing from the dramatic rise and productivity of biomedical research since World War II" led to "the view that the future of medical practice lay in subspecialty expertise and that generalists would lose capacity to manage serious or complex disease as the knowledge base of clinical medicine continued to expand"); Fred G. Donini-Lenhoff & Hannah L. Hedrick, *Growth of Specialization in Graduate Medical Education*, 284 JAMA 1284, 1284, 1287–88 (2000) (identifying more than 100 specialties or subspecialties, and attributing this proliferation to advances in knowledge and technology); Edward J. Huth, *The Information Explosion*, 65 BULL. N.Y. ACAD. MED. 647, 651 (1989); *see also* Larry Culpepper & Thomas T. Gilbert, *Evidence and Ethics*, 353 LANCET 829, 830 (1999) (noting that specialists have more evidence at their disposal than general practitioners).

139. *See* Martin T. Donohoe, *Comparing Generalist and Specialty Care: Discrepancies, Deficiencies, and Excesses*, 158 ARCHIVES INTERNAL MED. 1596, 1600 (1998); Elbert S. Huang & Randall S. Stafford, *National Patterns in the Treatment of Urinary Tract Infections in Women by Ambulatory Care Physicians*, 162 ARCHIVES INTERNAL MED. 41 (2002); Edward J. Huth, Editorial, *The Underused Medical Literature*, 110 ANNALS INTERNAL MED. 99, 99 (1989); Jay Katz, *Why Doctors Don't Disclose Uncertainty*, HASTINGS CTR. REP., Feb. 1984, at 35, 39 ("Although specialization is to begin with an adaptive response to the vastness of medical knowledge,...it paradoxically makes a significant contribution of its own to a spurious sense of certainty.").

140. *See* David G. Covell et al., *Information Needs in Office Practice: Are They Being Met?*, 103 ANNALS INTERNAL MED. 596, 598–99 (1985) ("Answers to questions raised at the time of the patient visit were found only 30% of the time; in a typical half day of office practice, four management decisions might have been altered if needed

less than optimal choices when one could have located additional information makes this context quite different from consumer purchasing decisions.[141] Patterns of inappropriate use may create serious risks of iatrogenic (treatment-induced) injury or represent foregone opportunities to improve patient outcomes.[142] In one widely publicized recent incident, a healthy volunteer who had enrolled in an asthma study at Johns Hopkins University died after taking hexamethonium, a drug associated with serious respiratory side effects apparently unknown to the researcher even though previously reported in the literature.[143]

3. Coping with Conflicts of Interest

In recent years, private funding of the generation and distribution of biomedical information has become a significant source of controversy. On the one hand, producers of medical technologies have the resources and incentives to sponsor expensive biomedical research. On the other hand, these companies

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information had been available at the time of the patient visit."); Allan M. Greenspan et al., *Incidence of Unwarranted Implantation of Permanent Cardiac Pacemakers in a Large Medical Population*, 318 NEW ENG. J. MED. 158, 161 (1988) ("[A] principal problem contributing to unnecessary [pacemaker] implantation may be inadequate physician education."); Jerome A. Osheroff et al., *Physicians' Information Needs: Analysis of Questions Posed During Clinical Teaching*, 114 ANNALS INTERNAL MED. 576, 578–80 (1991); Mark V. Pauly, *Practice Guidelines: Can They Save Money? Should They?*, 23 J.L. MED. & ETHICS 65, 68 (1995) ("[T]he costliness of a physician's time may make it rational for him...to avoid dealing with gratuitously given information. It is usually not efficient to pay much attention to information that falls from the sky."); *see also* Eric E. Fortess & Marshall B. Kapp, *Medical Uncertainty, Diagnostic Testing, and Legal Liability*, 13 LAW MED. & HEALTH CARE 213, 213 (1985); Richard Smith, *What Clinical Information Do Doctors Need?*, 313 BRIT. MED. J. 1062 (1996).

141. *See* Lucian L. Leape, *Error in Medicine*, 272 JAMA 1851, 1853–54 (1994); *see also* Kenneth J. Arrow, *Uncertainty and the Welfare Economics of Medical Care*, 53 AM. ECON. REV. 941, 966 (1963). *But cf.* Jerome P. Kassirer & Stephen G. Pauker, Editorial, *The Toss-Up*, 305 NEW ENG. J. MED. 1467, 1468–69 (1981) (suggesting that most difficult choices do not result in different clinical outcomes).

142. *See* Mark R. Chassin et al., *The Urgent Need to Improve Health Care Quality*, 280 JAMA 1000, 1002–03 (1998) (describing patterns of underuse, overuse, and misuse, and attributing these problems in part to the "avalanche of rigorous data on efficacy" and the fact that "too few physicians have ready access to all the data that would be useful to them as they care for patients"); Harry Hemingway et al., *Underuse of Coronary Revascularization Procedures in Patients Considered Appropriate Candidates for Revascularization*, 344 NEW ENG. J. MED. 645, 652–53 (2001); Gerald T. O'Connor et al., *Geographic Variation in the Treatment of Acute Myocardial Infarction: The Cooperative Cardiovascular Project*, 281 JAMA 627, 632 (1999) ("These gaps between knowledge and practice have important consequences."); Stephen B. Soumerai et al., *Adverse Outcomes of Underuse of β-Blockers in Elderly Survivors of Acute Myocardial Infarction*, 277 JAMA 115, 119–20 (1997).

143. *See* Jonathan Bor & Tom Pelton, *U.S. Halts Hopkins Research*, BALT. SUN, July 20, 2001, at 1A (reporting that the NIH's Office for Human Research Protection had found that "the scientist failed to discover published reports of toxic effects that were readily available on the Internet and in recent textbooks").

expect a return on their investment. In particular, industry has forged increasingly close ties with academia,[144] in what one could describe as the emergence of a "medical-industrial complex,"[145] reminiscent of the so-called "military-industrial complex" of an earlier generation. This creates the potential for serious conflicts of interest.[146]

Biases and conflicts of interest may arise at several points in the publication process. Perhaps the most obvious problem exists where the author of a manuscript has undertaken the research on behalf of a company or has a direct commercial stake in the outcome of the study. Subtle biases may influence the outcome of studies financed by the industry.[147] Numerous surveys have found that research on new drugs is more likely to turn out favorably when sponsored by the manufacturer.[148] In 1998, responding to such concerns, the FDA issued new rules

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144. *See* David Blumenthal et al., *Relationships Between Academic Institutions and Industry in the Life Sciences-An Industry Survey*, 334 NEW ENG. J. MED. 368, 372 (1996); Sheldon Krimsky et al., *Academic-Corporate Ties in Biotechnology: A Quantitative Study*, 16 SCI. TECH. & HUMAN VALUES 275, 285–86 (1991); Joseph B. Martin & Dennis L. Kasper, *In Whose Best Interest? Breaching the Academic-Industrial Wall*, 343 NEW ENG. J. MED. 1646 (2000); Hamilton Moses III & Joseph B. Martin, *Academic Relationships with Industry: A New Model for Biomedical Research*, 285 JAMA 933, 933 (2001) ("The network connecting academic laboratories, academic institutions, and companies is growing denser, more complex, and much more lucrative for all involved."); Goldie Blumenstyk & David L. Wheeler, *Academic Medical Centers Race to Compete in the $3.2 Billion Drug-Testing Market*, CHRON. HIGHER EDUC., Mar. 20, 1998, at A39.

145. *See* Editorial, *Drug-Company Influence on Medical Education in USA*, 356 LANCET 781, 781 (2000). *See generally* STANLEY WOHL, THE MEDICAL INDUSTRIAL COMPLEX (1984).

146. *See* Marcia Angell, Editorial, *Is Academic Medicine for Sale?*, 342 NEW ENG. J. MED. 1516, 1517 (2000); Catherine D. DeAngelis, Editorial, *Conflict of Interest and the Public Trust*, 284 JAMA 2238, 2238 (2000); Jerome P. Kassirer, *Financial Conflicts of Interest: An Unresolved Ethical Frontier*, 27 AM. J.L. & MED. 149 (2001); David Korn, *Conflicts of Interest in Biomedical Research*, 284 JAMA 2234 (2000); Robert Tomsho, *Medical-Research Rules Need Changes on Conflicts of Interest, Studies Assert*, WALL ST. J., Nov. 30, 2000, at A4.

147. *See* United States v. Univ. of Pittsburgh, 192 F.3d 402, 407 (3d Cir. 1999) (crediting the explanation by the chair of an NIH review committee "that a researcher who receives substantial funding from a pharmaceutical company can be subtly biased in favor of finding that the company's drugs are effective"); Arnold S. Relman, Editorial, *Economic Incentives in Clinical Investigations*, 320 NEW ENG. J. MED. 933, 933 (1989) ("Economic incentives can introduce subtle biases into the conduct, analysis, or reporting of research results that may escape even careful peer review."); Sidney A. Shapiro, *Divorcing Profit Motivation from New Drug Research: A Consolidation of Proposals to Provide the FDA with Reliable Test Data*, 1978 DUKE L.J. 155, 161–68; *id.* at 163 ("[T]he relationship between the sponsor and its researchers may have the effect of subtly biasing the results of studies in favor of drugs being tested...."). Although far less common, industry sponsorship of research by law professors has raised similar concerns. *See* Elizabeth Amon, *Exxon Bankrolls Critics of Punitives*, NAT'L L.J., May 17, 1999, at A1.

148. *See* Richard A. Davidson, *Source of Funding and Outcome of Clinical Trials*, 1 J. GEN. INTERNAL MED. 155, 156–57 (1986); Paula A. Rochon et al., *A Study of Manufacturer-Supported Trials of Nonsteroidal Anti-Inflammatory Drugs in the Treatment*

to require that sponsoring companies disclose any significant direct or indirect financial ties to the researchers who conduct clinical trials designed to demonstrate the safety and efficacy of an investigational product.[149]

Most journals also now require that authors disclose any potential conflicts of interest,[150] and some of these disclosures reveal truly remarkable linkages between researchers and drug companies,[151] but problems persist.[152] For instance, a survey of seventy recent journal articles concerning calcium channel blockers found that ninety-six percent of the authors defending their safety had financial relationships with the manufacturers of these drugs, many of which had not been disclosed in the published articles.[153] Although conscientious researchers

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of Arthritis, 154 ARCHIVES INTERNAL MED. 157, 161–62 (1994); Dan Vergano, *Drug Trials Vex Medical Ethics*, USA TODAY, Aug. 8, 2000, at 9D (describing research finding "that studies sponsored by drug companies reported negative results with drugs 5% of the time, vs. 38% in efforts financed by other sources").

149. *See* 63 Fed. Reg. 5233, 5250 (Feb. 2, 1998) (codified at 21 C.F.R. pt. 54 (2001)).

150. *See* George D. Lundberg & Annette Flanagin, *New Requirements for Authors: Signed Statements of Authorship Responsibility and Financial Disclosure*, 262 JAMA 2003, 2004 (1989); Int'l Comm. of Med. Journal Editors, *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, 108 ANNALS INTERNAL MED. 258, 260 (1988) (calling on authors to disclose any "financial relationships that may pose a conflict of interest"); *cf.* Michael S. Wilkes & Richard L. Kravitz, *Policies, Practices, and Attitudes of North American Medical Journal Editors*, 10 J. GEN. INTERNAL MED. 443, 448 (1995) (reporting significant variations in disclosure policies and practices).

151. *See* Cynthia Crossen, *A Medical Researcher Pays for Challenging Drug-Industry Funding*, WALL ST. J., Jan. 3, 2001, at A1 ("Since the early 1980s, connections in biomedicine between academics and drug companies have become so pervasive that a recent footnote to an article on antidepressants in the New England Journal of Medicine disclosed more than 350 financial ties between the authors of the article and pharmaceutical companies that sell antidepressants.").

152. *See* Sheldon Krimsky & L.S. Rothenberg, *Financial Interest and Its Disclosure in Scientific Publications*, 280 JAMA 225, 226 (1998) ("[J]ournal editors should begin to take seriously the implementation of disclosure policies in response to the escalation of financial interests of authors in their publications."); Sheryl Gay Stolberg, *Scientists Often Mum About Ties to Industry*, N.Y. TIMES, Apr. 25, 2001, at A15 (summarizing the results of a large-scale survey that suggested significant underreporting by authors of potential conflicts of interest); *see also* Constance Holden, *NEJM Admits Breaking Its Own Tough Rules*, 287 SCIENCE 1573, 1573 (2000); Laura Johannes, *Medical Editorialists May Have Failed to Disclose Tie to Obesity-Drug Maker*, WALL ST. J., Aug. 28, 1996, at B3 ("The New England Journal of Medicine is investigating whether two authors of a favorable editorial on a fast-selling new obesity drug inappropriately failed to disclose their consulting relationships with the companies that make and market the drug."); Janny Scott, *Researcher to Clarify Ties to Drug Manufacturer*, L.A. TIMES, Mar. 24, 1990, at B3 (describing the same type of incident at *JAMA*).

153. *See* Henry Thomas Stelfox et al., *Conflict of Interest in the Debate over Calcium-Channel Antagonists*, 338 NEW ENG. J. MED. 101, 103–04 (1998) (finding "a strong association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers"); Elyse

will not skew their data, one cannot dismiss the possibility that hopes for potentially lucrative funding of future research may influence their resolution of ambiguities in the data.[154] Similarly, scientists with ties to industry who are enlisted by editors to referee manuscripts also may harbor biases that color their recommendations for or against the publication of research conducted by others.[155]

Even if authors conscientiously adhered to the disclosure requirements, this mechanism for dealing with conflicts of interest may have only limited value.[156] First, because industry support has become so pervasive, readers may fail to pay any attention to these increasingly routine disclosures. Second, if readers do pay attention, how exactly should they take such information into account? Proponents of EBM have not suggested that RCTs sponsored by drug companies deserve less weight than other studies,[157] though perhaps such research should be read with extra skepticism. As explained in a subsequent section, physicians do a poor job of discounting the informational value of blatantly promotional materials, so it seems even less likely that they would harbor suspicions about published research funded by the industry. Finally, as suggested in the next two sections, disclosures appearing in published articles reporting on primary research will often get lost as the studies become absorbed into the secondary literature.

Some commentators also have expressed concerns that, by virtue of their tremendous expenditures for advertising in biomedical publications,[158]

Tanouye, *Does Corporate Funding Influence Research?*, WALL ST. J., Jan. 8, 1998, at B1 (summarizing these findings and initial reactions to their release).

154. *See* Mark Friedberg et al., *Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology*, 282 JAMA 1453, 1456 (1999) ("It is possible that these factors may result in some unconscious bias (perhaps when qualitatively interpreting results) that could influence study conclusions."). The study found that research sponsored by the pharmaceutical industry was more likely to reach favorable conclusions about the cost-effectiveness of drug interventions. *See id.* at 1455.

155. *See* Jeff Gerth & Sheryl Gay Stolberg, *Another Part of the Battle: Keeping a Drug in the Store*, N.Y. TIMES, Dec. 13, 2000, at A1 ("In scientific circles, a university pharmacologist acted as a reviewer for medical journals considering whether to publish reports on PPA [phenylpropanolamine], while he was on the payroll of the leading diet pill manufacturer....His anonymous critiques helped relegate some articles that questioned PPA's safety to little-known journals."); *see also* Marcia Angell & Jerome P. Kassirer, Editorial, *Editorials and Conflicts of Interest*, 335 NEW ENG. J. MED. 1055, 1055 (1996) (describing the spin that an editorial accompanying a study may reflect when authored by industry consultants).

156. *See* Dennis F. Thompson, *Understanding Financial Conflicts of Interest*, 329 NEW ENG. J. MED. 573, 575 (1993).

157. *See* Liz Trinder, *A Critical Appraisal of Evidence-Based Practice*, *in* EVIDENCE-BASED PRACTICE, *supra* note 81, at 212, 227. *But cf. Cochrance Reviewers' Handbook* § 6.7.1 (4.1.4 ed. Oct. 2001), *available at* http://www.cochrane.dk/cochrane/handbook/start.htm (last visited Apr. 1, 2002) (taking potential biases into account when assessing the quality of studies for inclusion in systematic reviews).

158. *See* Lawrence K. Altman, *Study Says Drug Ads in Medical Journals Frequently Mislead*, N.Y. TIMES, June 1, 1992, at A1 (reporting that drug companies spent $351 million on medical journal advertisements in 1991).

pharmaceutical manufacturers may unduly influence the judgments of journal editors.[159] Indeed, most journals accept advertisements only from sellers of health care products or services on the view that such advertisements serve an educational function.[160] Some commentators have proposed that, in order to reduce real or perceived conflicts of interest, biomedical journals should adopt precisely the opposite policy–namely, to accept advertising from sellers of health care products only as a last resort.[161] Their proposal has fallen on deaf ears. In fact, responding to the loss of advertising revenue that resulted when pharmaceutical companies shifted promotional campaigns to television, a group of biomedical

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159. *See* Lawrence K. Altman, *The Doctor's World: Hidden Discord Over Right Therapy*, N.Y. TIMES, Dec. 24, 1991, at C3 (describing the initial refusals to publish one researcher's dissent to the conclusions of his co-investigators that an antibiotic effectively treats ear infections, adding that "scientific journals profit handsomely from drug company advertisements, and the influence of industry on such publications has rarely been studied"); *see also* Richard A. Deyo et al., *The Messenger Under Attack—Intimidation of Researchers by Special-Interest Groups*, 336 NEW ENG. J. MED. 1176, 1179 (1997) (suggesting that journals may "need to set up defenses against potential threats of withholding advertising," adding that "[r]esearch on efficacy, safety, and cost effectiveness in the trillion-dollar health care industry frequently has important financial consequences"); *id.* at 1177:

> While the manuscript describing the study [which found that calcium channel blockers caused heart attacks] was under editorial review, pharmaceutical manufacturers tried to discover the identity of the journal to which it had been submitted, and it appeared to the investigators that opponents were trying to interfere with the publication of the study.

160. *See* Robert H. Fletcher & Suzanne W. Fletcher, Editorial, *Pharmaceutical Advertisements in Medical Journals*, 116 ANNALS INTERNAL MED. 951, 952 (1992). In denying one medical journal's request for a tax exemption for its advertising revenues, the Supreme Court questioned this educational rationale: "all advertisements contain some information, and if a modicum of informative content were enough to supply the important contribution necessary to achieve tax exemption for commercial advertising, it would be the rare advertisement indeed that would fail to meet the test." United States v. Am. Coll. of Physicians, 475 U.S. 834, 848 (1986); *see also id.* at 849–50 ("This is not to say that the [American] College [of Physicians] could not control its publication of advertisements in such a way as to reflect an intention to contribute importantly to its educational functions...[, perhaps] by publishing only advertisements reflecting new developments in the pharmaceutical market, for example...."); *cf. id.* at 850 (Burger, C.J., concurring) (arguing that at some point the IRS might choose to exempt such advertising from taxation because it helps to reduce the cost of publishing and circulating information important to the public health).

161. *See* David Orentlicher & Michael K. Hehir II, *Advertising Policies of Medical Journals: Conflicts of Interest for Journal Editors and Professional Societies*, 27 J.L. MED. & ETHICS 113, 113–16, 118 (1999). Responding to the objection that the loss of advertising revenue might lead to a reduction in the number of biomedical journals, the authors applauded such an outcome. *See id.* at 117 ("[C]urrently a very large number of medical journals are being published; hence one could argue that fewer journals would ensure that only studies of high quality are published."); *id.* at 120 n.42 ("Bad information can lead to dangerous therapies being used and harm being caused to patients. Having fewer journals will decrease the likelihood of a bad article being published, and patients may end up better overall.").

journals recently touted the results of a study finding that print ads targeted to health professionals provide companies with the most cost-effective available outlet for promotional messages.[162]

Editors have recognized the need to guard against industry influence, but they strenuously deny that the source of advertising revenues has had any impact on their publication decisions.[163] Interestingly, some journals have imposed stricter conflict of interest rules for outside authors of editorials,[164] presumably in recognition of the continuing influence exerted by "opinion leaders" in shaping medical practice. More direct forms of industry influence over editorial choices arise when pharmaceutical companies sponsor special symposium issues of a medical journal,[165] sometimes dubbed vanity press. One study of the phenomenon found that "industry-sponsored symposiums are promotional in nature and that journals often abandon the peer-review process when they publish symposiums."[166]

A still more serious concern is that companies sponsoring biomedical research will interfere directly in the reporting of study results. First, they may ghost write articles nominally authored by independent researchers.[167] Second,

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162. *See* Vanessa O'Connell, *Medical Journals Chase Drug-Ad Dollars*, WALL ST. J., May 22, 2001, at B8.

163. *See* Int'l Comm. of Med. Journal Editors, *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, 277 JAMA 927, 934 (1997) ("[A]dvertising must not be allowed to influence editorial decisions."); Drummond Rennie, Editorial, *Editors and Advertisements: What Responsibility Do Editors Have for the Advertisements in Their Journals?*, 265 JAMA 2394, 2395–96 (1991) (same).

164. *See* Arthur S. Relman, Editorial, *New "Information for Authors"—and Readers*, 323 NEW ENG. J. MED. 56, 56 (1990) (explaining editorial decision against even considering for publication review articles or editorials about a product if any author has a financial relationship with an interested manufacturer).

165. *See* Mildred K. Cho & Lisa A. Bero, *The Quality of Drug Studies Published in Symposium Proceedings*, 124 ANNALS INTERNAL MED. 485, 488 (1996); Paula A. Rochon et al., *Evaluating the Quality of Articles Published in Journal Supplements Compared with the Quality of Those Published in the Parent Journal*, 272 JAMA 108, 111–12 (1994) (finding that supplements included studies of inferior quality due to the lack of regular peer review).

166. Lisa A. Bero et al., *The Publication of Sponsored Symposiums in Medical Journals*, 327 NEW ENG. J. MED. 1135, 1137 (1992) ("Financial pressures on journals appear to contribute to the increasing publication of symposiums."). The authors of the study warned that "[s]ymposiums may be given more credence than they deserve, because they often resemble regular journal issues and may be presented as educational materials....The acceptance of symposium publications could distort the medical literature and ultimately alter physicians' prescribing practices and patient care." *Id.* at 1138.

167. *See* Annette Flanagin et al., *Prevalence of Articles with Honorary Authors and Ghost Authors in Peer-Reviewed Medical Journals*, 280 JAMA 222, 223–24 (1998) (finding that eleven percent of articles sampled had ghost authors); Doug Levy, *Ghostwriters a Hidden Resource for Drug Makers*, USA TODAY, Sept. 25, 1996, at 1A; *see also* Troyen A. Brennan, Letter, *Buying Editorials*, 331 NEW ENG. J. MED. 673 (1994) (describing one company's effort to enlist a researcher to sign his name to an editorial endorsing one of its drugs in exchange for an honorarium); Thomas Bodenheimer, *Uneasy*

they may attempt to block the publication of unfavorable study results.[168] In the last several years, a few pharmaceutical companies have attracted significant criticism for trying to squelch the publication of research that they had sponsored when they did not care for the conclusions.[169] If sponsors succeed in delaying or blocking publication of such negative results, this will undermine the post-publication error correction process and distort the secondary literature. As happens with publication bias, clinicians will be deprived of potentially important findings when making treatment decisions, and systematic reviews will fail to include these unflattering research results. In response to concerns about this form of "censorship," a dozen leading medical journals recently adopted a new policy designed to discourage this practice.[170]

B. Secondary Research

The broader peer review process continues long after an article appears in print. Post-publication peer review occurs most visibly in the production of the

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Alliance: Clinical Investigators and the Pharmaceutical Industry, 342 NEW ENG. J. MED. 1539, 1541–43 (2000).

168. *See* Drummond Rennie, Editorial, *Thyroid Storm*, 277 JAMA 1238 (1997) (describing increasing industry sponsorship of biomedical research, and criticizing efforts to control its publication); *see also* David Blumenthal et al., *Withholding Research Results in Academic Life Sciences: Evidence from a National Survey of Faculty*, 277 JAMA 1224, 1226 (1997) (reporting that some researchers had delayed publication of their studies "to slow dissemination of undesired results"); *see also* Sheryl Gay Stolberg, *Gifts to Science Researchers Have Strings Attached, Study Finds*, N.Y. TIMES, Apr. 1, 1998, at A13 (describing the results of a survey published in *JAMA* finding that "more than half of the university scientists who received gifts [such as cell lines or laboratory equipment] from drug or biotechnology companies admitted that the donors expected to exert influence over their work, including review of academic papers before publication"). When the NIH attempted to impose a similar condition on research grants to develop an artificial heart, a federal court held that the contract provision violated the Constitution. *See* Bd. of Trustees of Leland Stanford Jr. Univ. v. Sullivan, 773 F. Supp. 472 (D.D.C. 1991) (holding that the condition amounted to an impermissible prior restraint under the First Amendment, and rejecting the government's argument that the condition would protect public safety by preventing the premature publication of unvalidated research).

169. *See* Editorial, *The Tightening Grip of Big Pharma*, 357 LANCET 1141, 1141 (2001) (condemning the "[e]ffort by drug companies to suppress, spin, and obfuscate findings that do not suit their commercial purposes"); Lawrence K. Altman, *Drug Firm, Relenting, Allows Unflattering Study to Appear*, N.Y. TIMES, Apr. 16, 1997, at A1 (describing the long-delayed publication of a study sponsored by the manufacturer of the brand-name version of a thyroid drug that found no benefit over less expensive generic versions); David Brown, *Scientists Report Bid to Block Publication of an AIDS Study*, WASH. POST, Nov. 1, 2000, at A10 (describing a biotechnology company's effort to interfere with the publication of unfavorable results from a study that it had sponsored of its experimental AIDS vaccine).

170. *See* Frank Davidoff et al., *Sponsorship, Authorship, and Accountability*, 286 JAMA 1232, 1233 (2001) ("We will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication.").

secondary scientific literature, including textbooks and review articles.[171] Authors of such reference materials summarize and assess original research on a subject that has accumulated in the primary literature. This secondary literature becomes increasingly valuable as the primary research literature expands to an unmanageable size.[172] Also, as mentioned earlier, reports of particular clinical trials or epidemiological studies may conflict with one another,[173] which the secondary literature can highlight and perhaps resolve. In a sense, the secondary literature compiles information from the primary literature that has withstood the test of time,[174] though even this form of post-publication scrutiny provides little assurance if the authors of the secondary literature uncritically accept published reports and repeat their errors.[175]

In addition to narrative reviews that summarize previously reported research findings, some researchers use "meta-analysis" to pool the data from several smaller clinical trials in an effort to derive statistically significant results

171. *See* Cynthia D. Mulrow, *The Medical Review Article: State of the Science*, 106 ANNALS INTERNAL MED. 485, 485 (1987) ("Good review articles are precious commodities....Reduction of large quantities of information into palatable pieces is essential for digestion."); *see also* Lois Ann Colaianni, *Peer Review in Journals Indexed in Index Medicus*, 272 JAMA 156, 157 (1993) (explaining that some journals scrutinize review articles differently than original articles). For an example of a review article, see Phyllis A. Dennery et al., *Neonatal Hyperbilirubinemia*, 344 NEW ENG. J. MED. 581 (2001).

172. *See* Guyatt et al., *supra* note 35, at 1294 ("Time limitation remains the biggest obstacle to evidence-based practice....[C]linicians whose priority is efficient evidence-based practice should seek a high-quality systematic review rather than the primary studies addressing their clinical question."); Andrew D. Oxman et al., *Agreement Among Reviewers of Review Articles*, 44 J. CLINICAL EPIDEMIOLOGY 91, 97 (1991) ("Clinicians and other decision-makers should be encouraged to rely on scientifically sound research overviews as an effective and efficient means of processing large amounts of information."). *See generally* SYSTEMATIC REVIEWS: SYNTHESIS OF BEST EVIDENCE FOR HEALTH CARE DECISIONS (Cynthia Mulrow & Deborah Cook eds., 1998); Andrew D. Oxman et al., *Users' Guides to the Medical Literature: VI. How to Use an Overview*, 272 JAMA 1367 (1994).

173. *See* Marcia Angell & Jerome P. Kassirer, Editorial, *Clinical Research–What Should the Public Believe?*, 331 NEW ENG. J. MED. 189, 189–90 (1994); Ralph I. Horwitz, *Complexity and Contradiction in Clinical Trial Research*, 82 AM. J. MED. 498, 499 (1987); *see also supra* notes 64–65 and accompanying text.

174. *See* Elliot M. Antman et al., *A Comparison of Results of Meta-Analyses of Randomized Control Trials and Recommendations of Clinical Experts: Treatments for Myocardial Infarction*, 268 JAMA 240, 246–47 (1992) (reporting delays of several years before published off-label uses of drugs are widely accepted in medical textbooks and other secondary literature); *see also* HENRY H. BAUER, SCIENTIFIC LITERACY AND THE MYTH OF THE SCIENTIFIC METHOD 46 (1992) ("[I]n physics, textbook science may be about 90 percent right, whereas the primary literature is probably 90 percent wrong.").

175. *See* PETR SKRABANEK & JAMES MCCORMICK, FOLLIES AND FALLACIES IN MEDICINE 40 (1990) ("In the current medical textbooks, two specialty monographs, and also in a standard pharmacopoeia, it is said that phenytoin, a drug commonly used to control fits, can cause red urine if the urine is acid. [Researchers] traced this myth to a reference in a pharmacy journal."). *See generally* MAX MICHAEL ET AL., BIOMEDICAL BESTIARY: AN EPIDEMIOLOGIC GUIDE TO FLAWS AND FALLACIES IN THE MEDICAL LITERATURE (1984).

from this pre-existing research base.[176] Successful meta-analysis requires that the underlying clinical trials resemble one another fairly closely and not suffer from their own methodological flaws.[177] Even if one can surmount this quite significant obstacle, however, disputes continue about the value of meta-analysis. In some instances, meta-analyses of several smaller RCTs reached results that conflicted with subsequently completed large-scale RCTs, which casts some doubt on the methodology of pooling clinical trials that individually fail to reach statistically significant results.[178] For these reasons, perhaps one should characterize meta-analyses as part of the primary rather than secondary literature.

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176. *See* Deborah J. Cook et al., *Systematic Reviews: Synthesis of Best Evidence for Clinical Decisions*, 126 ANNALS INTERNAL MED. 376, 377 (1997) ("Systematic reviews represent the best chance that most practitioners will have to understand and accurately apply the key signals arising from the robust and increasingly productive search for solutions to medical problems."); Matthias Egger & George Davey-Smith, *Meta-Analysis: Potentials and Promise*, 315 BRIT. MED. J. 1371 (1997); Henry S. Sacks et al., *Meta-Analyses of Randomized Controlled Trials*, 316 NEW ENG. J. MED. 450, 454 (1987) (concluding that, if properly conducted, "a quantitative synthesis of the data in similar randomized controlled trials can potentially be more useful to the practicing physician than a traditional review article"); Stephen B. Thacker, *Meta-Analysis: A Quantitative Approach to Research Integration*, 259 JAMA 1685 (1988). *See generally* DIANA B. PETITTI, META-ANALYSIS, DECISION ANALYSIS, AND COST-EFFECTIVENESS ANALYSIS: METHODS FOR QUANTITATIVE SYNTHESIS IN MEDICINE (2d ed. 2000).

177. *See* Khalid S. Khan et al., *The Importance of Quality of Primary Studies in Producing Unbiased Systematic Reviews*, 156 ARCHIVES INTERNAL MED. 661, 666 (1996); David Moher & Ingram Olkin, *Meta-Analysis of Randomized Controlled Trials: A Concern for Standards*, 274 JAMA 1962 (1995); Kenneth F. Schulz et al., *Empirical Evidence of Bias: Dimensions of Methodological Quality Associated with Estimates of Treatment Effects in Controlled Trials*, 273 JAMA 408, 410–12 (1995); Salim Yusuf, *Obtaining Medically Meaningful Answers from an Overview of Randomized Clinical Trials*, 6 STAT. MED. 281, 285 (1987).

178. *See* Steven Borzak & Paul M. Ridker, *Discordance Between Meta-Analyses and Large-Scale Randomized, Controlled Trials: Examples from the Management of Acute Myocardial Infarction*, 123 ANNALS INTERNAL MED. 873, 874–76 (1995); Michael J. Domanski & Lawrence M. Friedman, Editorial, *Relative Role of Meta-Analysis and Randomized Controlled Trials in the Assessment of Medical Therapies*, 74 AM. J. CARDIOLOGY 395, 396 (1994); Matthias Egger et al., *Bias in Meta-Analysis Detected by a Simple, Graphical Test*, 315 BRIT. MED. J. 629 (1997); Jacques LeLorier et al., *Discrepancies Between Meta-Analyses and Subsequent Large Randomized, Controlled Trials*, 337 NEW ENG. J. MED. 536, 539–41 (1997); C. David Naylor, Editorial, *Meta-Analysis and the Meta-Epidemiology of Clinical Research*, 315 BRIT. MED. J. 617 (1997); *see also* Robert Temple, *Problems in the Use of Large Data Sets to Assess Effectiveness*, 6 INT'L J. TECH. ASSESSMENT IN HEALTH CARE 211, 211 (1990) (expressing concerns that meta-analyses will not always get checked in this way); *cf.* Joseph C. Cappelleri et al., *Large Trials vs. Meta-Analyses of Smaller Trials: How Do Their Results Compare?*, 276 JAMA 1332, 1336–37 (1996) (concluding that large RCTs usually confirm earlier meta-analyses); John P.A. Ioannidis et al., *Issues in Comparisons of Meta-Analyses and Large Trials*, 279 JAMA 1089, 1093 (1998).

Cost-effectiveness analysis represents another hybrid.[179] An extension of outcomes research, these studies attempt to quantify the benefits of a particular course of treatment, for instance by using safety and efficacy data from RCTs for different methods of treating the same condition in an effort to make a comparative assessment. Like meta-analyses, these comparative studies continue to generate sharp methodological disputes.[180] "Pharmacoeconomics," which attempts to document the cost effectiveness of drugs, has attracted particular criticism.[181] Concerns about conflicts of interest become even more pronounced in this context,[182] and pharmaceutical manufacturers may stack the deck when they design comparative studies in an effort to ensure a favorable result.[183]

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179. *See* Jerome P. Kassirer & Marcia Angell, Editorial, *The* Journal's *Policy on Cost-Effectiveness Analyses*, 331 NEW ENG. J. MED. 669, 669 (1994) ("[T]hey are like review articles in that the assumptions made in constructing the models and the data used in the analysis are usually chosen selectively from the literature, and the choices could be biased.").

180. *See* Michael F. Drummond et al., *Users' Guides to the Medical Literature: XIII. How to Use an Article on Economic Analysis of Clinical Practice: A. Are The Results of the Study Valid?*, 277 JAMA 1552 (1997); Finlay A. McAlister et al., *Users' Guides to the Medical Literature: XIX. Applying Clinical Trial Results: B. Guidelines for Determining Whether a Drug Is Exerting (More Than) a Class Effect*, 282 JAMA 1371, 1372–75 (1999); Louise B. Russell et al., *The Role of Cost-Effectiveness Analysis in Health and Medicine*, 276 JAMA 1172, 1176 (1996); I. Steven Udvarhelyi et al., *Cost-Effectiveness and Cost-Benefit Analyses in the Medical Literature: Are the Methods Being Used Correctly?*, 116 ANNALS INTERNAL MED. 238, 241–43 (1992); Milton C. Weinstein et al., *Recommendations of the Panel on Cost-Effectiveness in Health and Medicine*, 276 JAMA 1253, 1258 (1996).

181. *See* Suzanne R. Hill et al., *Problems with the Interpretation of Pharmacoeconomic Analyses*, 283 JAMA 2116, 2120–21 (2000) ("We doubt whether any conventional peer-review process is adequate."); Drummond Rennie & Harold S. Luft, Editorial, *Pharmacoeconomic Analyses: Making Them Transparent, Making Them Credible*, 283 JAMA 2158, 2158–59 (2000). *But cf.* Peter J. Neumann & Darren E. Zinner, *Evaluating and Regulating Pharmacoeconomic Information in the Private Sector*, 32 DRUG INFO. J. 525, 529–30 (1998) (suggesting that editorial peer review can address these concerns adequately).

182. *See* Robert G. Evans, Editorial, *Manufacturing Consensus, Marketing Truth: Guidelines for Economic Evaluation*, 123 ANNALS INTERNAL MED. 59, 59 (1995); Kassirer & Angell, *supra* note 179, at 669–70 (explaining the *New England Journal of Medicine*'s editorial decision against even considering cost effectiveness studies for publication if any author has a personal financial stake in the outcome, and requiring disclosure of industry sponsorship of such studies when conducted by independent researchers); Peter J. Neumann et al., *Are Pharmaceuticals Cost-Effective? A Review of the Evidence*, HEALTH AFF., Mar.–Apr. 2000, at 92, 99–101; *see also* Relman, *supra* note 147, at 933 ("[Financial] incentives can also bias review articles and public statements by clinical investigators about their work, which in turn may have important effects on the clinical decisions of practicing physicians."); Friedberg, *supra* note 154.

183. *See* Lisa A. Bero & Drummond Rennie, *Influences on the Quality of Published Drug Studies*, 12 INT'L J. TECH. ASSESSMENT IN HEALTH CARE 209, 217, 221, 228 (1996); Alan L. Hillman et al., *Avoiding Bias in the Conduct and Reporting of Cost-Effectiveness Research Sponsored by Pharmaceutical Companies*, 324 NEW ENG. J. MED. 1362, 1363–64 (1991); Helle Krogh Johansen & Peter C. Gøtzsche, *Problems in the Design*

Review articles and textbooks, however derived, may become dated rapidly unless revised to incorporate the latest research.[184] In response to such concerns, a mechanism has emerged to provide health care providers with up-to-date reviews of the primary literature. The Cochrane Collaboration, produced by an international network headquartered in Oxford, England, uses an electronic format to provide frequently updated systematic reviews of biomedical research based on strict methodological guidelines and using a standardized reporting format.[185] Such sources offer practitioners important advantages over traditional literature reviews. For instance, not until after the Cochrane Collaboration drew attention to several published RCTs demonstrating the value of corticosteroids in premature births did most obstetricians begin to administer the drug to patients.[186]

C. Practice Guidelines

Clinical practice guidelines–also sometimes called practice parameters, algorithms, or clinical pathways–represent highly structured efforts to distill the available research and translate it for use by physicians in the care of patients.[187]

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and Reporting of Trials of Antifungal Agents Encountered During Meta-Analysis, 282 JAMA 1752, 1757–58 (1999); Susan Okie, *Missing Data on Celebrex: Full Study Altered Picture of Drug*, WASH. POST, Aug. 5, 2001, at A11.

184. *See* Antman et al., *supra* note 174, at 245–47 (finding that the recommendations appearing in medical textbooks may lag behind new empirical evidence by as much as a decade); Jeremy Wyatt, *Use and Sources of Medical Knowledge*, 338 LANCET 1368, 1371 (1991).

185. *See* Lisa Bero & Drummond Rennie, *The Cochrane Collaboration: Preparing, Maintaining, and Disseminating Systematic Reviews of the Effects of Health Care*, 274 JAMA 1935 (1995); Alejandro R. Jadad et al., *Methodology and Reports of Systematic Reviews and Meta-Analyses: A Comparison of Cochrane Reviews with Articles Published in Paper-Based Journals*, 280 JAMA 278, 278–79 (1998); Alejandro R. Jadad et al., *Systematic Reviews and Meta-Analysis on Treatment of Asthma: A Critical Analysis*, 320 BRIT. MED. J. 537, 539–40 (2000); *see also* Joseph Lau et al., *Cumulative Meta-Analysis of Clinical Trials Builds Evidence for Exemplary Medical Care*, 48 J. CLINICAL EPIDEMIOLOGY 45, 56 (1995) (describing a method for continually updating meta-analyses to reflect the results of new RCTs). Recently, biomedical journals have made efforts to standardize the format for reporting the results of clinical trials. *See* Colin Begg et al., *Improving the Quality of Reporting of Randomized Controlled Trials: The CONSORT Statement*, 276 JAMA 637 (1996); Kenneth F. Schulz, *Randomised Trials, Human Nature, and Reporting Guidelines*, 348 LANCET 596 (1996); Asilomar Working Group, *Checklist of Information for Inclusion in Reports of Clinical Trials*, 124 ANNALS INTERNAL MED. 741 (1996).

186. *See* Gary Taubes, *Looking for the Evidence in Medicine*, 272 SCIENCE 22, 22–23 (1996). *But cf.* Edward E. Lawson, Editorial, *Antenatal Corticosteroids—Too Much of a Good Thing?*, 286 JAMA 1628 (2001) (giving the credit to a 1994 NIH Consensus Conference, and explaining that practice recommendations on this subject continue to evolve in light of new research findings).

187. *See* Maxwell J. Mehlman, *Assuring the Quality of Medical Care: The Impact of Outcome Measurement and Practice Standards*, 18 LAW MED. & ETHICS 368, 376 (1990) ("Ideally, practice standards reflect expert consensus based on a combination of experience and an evaluation of the data available in the scientific literature. Referring to standards

Inspired initially by seemingly inexplicable geographic variations in practice patterns,[188] they combine basic biomedical investigations with health care outcomes research. David Eddy, one of the earliest proponents of clinical practice guidelines, offered the following assessment:

> They can connect each practitioner to a collective consciousness, bringing order, direction, and consistency to their decisions. Practice policies provide an intellectual vehicle through which the profession can distill the lessons of research and clinical experiences and pool the knowledge and preferences of many people into conclusions about appropriate practices. They provide a natural pathway to convey that information to practitioners. Practice policies are the central nervous system of medical practice.[189]

The "collective consciousness" that Dr. Eddy envisioned seems quite different, however, from that described by Foucault.[190]

Clinical practice guidelines can serve an important role in disseminating information. In both their scope and the rigor of peer scrutiny, these guidelines typically go beyond textbooks and review articles published in the biomedical journals.[191] Putting aside occasional complaints that they represent an affront to

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therefore can avoid errors that might result from ignorance of the current literature or lack of experience."); Arnold J. Rosoff, *The Role of Clinical Practice Guidelines in Health Care Reform*, 5 HEALTH MATRIX 369, 375 (1995) ("[A]s the body of what is knowable and what is known grows, the degree of latitude [for the exercise of professional judgment] will inevitably be impacted by the extant knowledge base....Knowledge brings limitations, or at least, the basis for limitations to be imposed."); John H. Wasson et al., *Clinical Prediction Rules: Applications and Methodological Standards*, 313 NEW ENG. J. MED. 793, 793 (1985).

188. *See* Mark R. Chassin et al., *Variations in the Use of Medical and Surgical Services by the Medicare Population*, 314 NEW ENG. J. MED. 285, 287–89 (1986); Paul D. Cleary et al., *Variations in Length of Stay and Outcomes for Six Medical and Surgical Conditions in Massachusetts and California*, 266 JAMA 73, 79 (1991); David L. Schriger et al., *The Origins, Benefits, Harms, and Implications of Emergency Medicine Clinical Policies*, 22 ANNALS EMERGENCY MED. 597, 598 (1993) ("The guidelines movement seeks to decrease the amount of variation in medical care by educating and encouraging physicians to use those processes that have been demonstrated (or are strongly felt) to lead to better patient outcomes."); *see also* Dan Vergano, *South, Midwest Use More Prescribed Drugs*, USA TODAY, Jan. 7, 2002, at 4D (reporting that similar geographic variations exist in prescribing patterns).

189. David M. Eddy, *Practice Policies—What Are They?*, 263 JAMA 877, 878 (1990); *see also id.* at 880 ("It is not stretching things too far to say that whoever controls practice policies controls medicine."); Lucian L. Leape, *Practice Guidelines and Standards: An Overview*, 16 QUALITY REV. BULL. 42, 46 (1990) ("Practice guidelines thus typically represent a marriage of evidence, experience, and opinion.").

190. *See* Foucault, *supra* note 12.

191. *See* KENNETH R. FOSTER & PETER W. HUBER, JUDGING SCIENCE: SCIENTIFIC KNOWLEDGE AND THE FEDERAL COURTS 186 (1997) ("The great care that consensus groups take in reviewing reports stands in sharp contrast to the often haphazard review process of

professional autonomy and promote "cook book" medicine,[192] physicians appear to appreciate these documents as another source of useful information.[193] If nothing else, practice guidelines provide a handy abridgment of the burgeoning biomedical literature.[194] They also serve a signaling function, reflecting the judgments of leading experts in the field.

More than 2000 guidelines exist today.[195] The increasing popularity of such guidelines represents something of a triumph for proponents of evidence-

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scientific journals."); Deborah J. Cook et al., *The Relation Between Systematic Reviews and Practice Guidelines*, 127 ANNALS INTERNAL MED. 210, 211–13 (1997).

192. *See* Matthew H. Liang, *Cookbook Medicine or Food for Thought: Practice Guidelines Development in the USA*, 51 ANNALS RHEUMATIC DISEASES 1257, 1258 (1992) (noting that doctors "have traditionally been resistant to reductionist approaches to the practice of medicine"); Edward Felsenthal, *Cookbook Care: Maine Limits Liability for Doctors Who Meet Treatment Guidelines*, WALL ST. J., May 3, 1993, at A1 ("Many physicians attack checklists as paint-by-numbers medicine that ignores the idiosyncracies of patients' conditions.").

193. *See* Robert H. Brook, *Practice Guidelines and Practicing Medicine: Are They Compatible?*, 262 JAMA 3027, 3028 (1989); Sean R. Tunis et al., *Internists' Attitudes About Clinical Practice Guidelines*, 120 ANNALS INTERNAL MED. 956, 961 (1994) ("We found that most [American College of Physicians] members have positive attitudes about guidelines in general, perceiving them to be of educational value and likely to improve the quality of patient care."); *see also* MARC BERG, RATIONALIZING MEDICAL WORK: DECISION-SUPPORT TECHNIQUES AND MEDICAL PRACTICES (1997); Carmi Z. Margolis et al., *Clinical Algorithms Teach Pediatric Decisionmaking More Effectively Than Prose*, 27 MED. CARE 576, 581–83 (1989) (suggesting that a flow chart format facilitates learning by physicians).

194. *See* Deborah W. Garnick et al., *Can Practice Guidelines Reduce the Number and Costs of Malpractice Claims?*, 266 JAMA 2856, 2857 (1991) ("The explosion of medical information and the increased complexity in today's health care system have made this support necessary. Physicians have been shown to have difficulty incorporating large amounts of information into their practice decisions."); Jodi Halpern, *Can the Development of Practice Guidelines Safeguard Patient Values?*, 23 J.L. MED. & ETHICS 75, 75–76 (1995) ("Guidelines are helpful because they enable physicians to move from making judgments based on their own relatively limited experience and reading to judgments based on expert experience and comprehensive reviews of the ever-expanding medical literature."); Laura Landro, *Health Advocates Seek Guidelines That Stick to Proven Treatments*, WALL ST. J., May 11, 2001, at B1 (reporting one expert's comment that "guidelines will help doctors to stay on top of the explosion in new data from clinical trials and medical research").

195. *See* GENERAL ACCOUNTING OFFICE, PRACTICE GUIDELINES: MANAGED CARE PLANS CUSTOMIZE GUIDELINES TO MEET LOCAL INTERESTS, No. HEHS-96-95 (1996), at 3 (adding that approximately seventy-five organizations have authored such guidelines); *see also* MEDICAL OUTCOMES AND GUIDELINES SOURCEBOOK (Laura Newman et al. eds., 1999); John T. Kelly & Margaret C. Toepp, *Practice Parameters: Development, Evaluation, Dissemination, and Implementation*, 18 QUALITY REV. BULL. 405, 405 (1992); Steven H. Woolf, *Practice Guidelines: A New Reality in Medicine: I. Recent Developments*, 150 ARCHIVES INTERNAL MED. 1811, 1817 (1990). These guidelines can, however, cover only a small range of all possible treatment situations. *See* Robert W. Dubois & Robert H. Brook, *Assessing Clinical Decision Making: Is the Ideal System Feasible?*, 25 INQUIRY 59, 63 (1988) (estimating that a reasonably comprehensive set of protocols would require billions of entries).

based medicine.[196] As the Institute of Medicine explained, practice guidelines "can be seen as part of a significant cultural shift, a move away from unexamined reliance on professional judgment toward more structured support and accountability for such judgment."[197] Clinical practice guidelines are not, however, synonymous with EBM, which represents something of a shift away from the more traditional consensus-based, experiential approach to medicine.[198] Practice guidelines can facilitate EBM, but clinicians must know how to distinguish high quality guidelines from ones of a lesser caliber.[199]

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196. *See* David M. Eddy, *Practice Policies—Guidelines for Methods*, 263 JAMA 1839, 1840–41 (1990); Gray Ellrodt et al., *Evidence-Based Disease Management*, 278 JAMA 1687, 1689 (1997); Jonathan Lomas et al., *The Role of Evidence in the Consensus Process: Results from a Canadian Consensus Exercise*, 259 JAMA 3001, 3004 (1988); *see also* Kathleen N. Lohr, *Guidelines for Clinical Practice: What They Are and Why They Count*, 23 J.L. MED. & ETHICS 49, 50 (1995) ("Over the decades, it is probably fair to estimate that several thousand 'guidelines-like' statements and documents have been produced, but it is also fair to say that most do not measure up to basic criteria such as being science-based, documented, unbiased, and clear.").

197. INSTITUTE OF MEDICINE, CLINICAL PRACTICE GUIDELINES: DIRECTIONS FOR A NEW PROGRAM 2 (Marilyn J. Field & Kathleen N. Lohr eds., 1990); *see also* INSTITUTE OF MEDICINE, GUIDELINES FOR CLINICAL PRACTICE: FROM DEVELOPMENT TO USE 24 (Marilyn J. Field & Kathleen N. Lohr eds., 1992) ("[M]any physicians, especially those longer in practice, see guidelines as a challenge to clinical judgment and resist them as a threat to the most fundamental element of professional autonomy....Generational change, which obviously takes time, should lead to some greater acceptance of standardized, science-based guidelines...."); Toby Lipman, *Evidence-Based Practice in General Practice and Primary Care*, *in* EVIDENCE-BASED PRACTICE, *supra* note 81, at 35, 53 (explaining that practitioners may resist EBM because it forces them to become students again).

198. *See* Eisenberg, *supra* note 41, at 369 (explaining that EBM "challenges consensus-based judgments"); Arnold J. Rosoff, *Evidence-Based Medicine and the Law: The Courts Confront Clinical Practice Guidelines*, 26 J. HEALTH POL., POL'Y & L. 327, 328–29 (2001); *see also* Gordon H. Guyatt et al., *Users' Guides to the Medical Literature: XVI. How to Use a Treatment Recommendation*, 281 JAMA 1836, 1838 (1999).

199. *See* Guyatt et al., *supra* note 35, at 1294 ("Increasingly, clinicians...can look to high-quality evidence-based practice guidelines or clinical pathways to provide, in effect, a series of synopses that summarize available evidence."); Robert S.A. Hayward et al., *More Informative Abstracts of Articles Describing Clinical Practice Guidelines*, 118 ANNALS INTERNAL MED. 731, 731 (1993) ("[Guidelines] could help physicians deal with the information overload they face. Existing practice guidelines, however, vary widely in their quality...."); Clement J. McDonald & J. Marc Overhage, Editorial, *Guidelines You Can Follow and Can Trust: An Ideal and an Example*, 271 JAMA 872 (1994); W. Scott Richardson et al., *Users' Guides to the Medical Literature: VII. How to Use a Clinical Decision Analysis: B. What Are the Results and Will They Help Me in Caring for My Patients?*, 273 JAMA 1610, 1611 (1995); Mark C. Wilson et al., *Users' Guides to the Medical Literature: VIII. How to Use Clinical Practice Guidelines: B. What Are the Recommendations and Will They Help You in Caring for Your Patients?*, 274 JAMA 1630, 1631 (1995).

The formulation of clinical practice guidelines is not simply a scientific exercise.[200] One might draw a parallel to the process used by the American Law Institute (ALI) when drafting its *Restatements of the Law*, which increasingly resembles a political rather than an academic debate.[201] Similarly, stakeholders have tried to influence the development of diagnostic guidelines issued by medical associations.[202] Some researchers have attempted to model the consensus-building process that underlies the development of clinical practice guidelines, which may employ special procedures for polling expert panels for an assessment of the appropriateness of using particular procedures in a series of hypothetical scenarios,[203] but this still does not convert it into a scientific endeavor: "A

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200. *See* Ken Marcus Gatter, *The Continued Existence and Benefit of Medicine's Autonomous Law in Today's Health Care System*, 24 U. DAYTON L. REV. 215, 238–39 (1999); David C. Hadorn, *Emerging Parallels in the American Health Care and Legal-Judicial Systems*, 18 AM. J.L. & MED. 73, 88 (1992); *cf.* Lars Noah, *Scientific "Republicanism": Expert Peer Review and the Quest for Regulatory Deliberation*, 49 EMORY L.J. 1033, 1045–52, 1072–74, 1083 (2000) (explaining that the process of seeking advice from independent experts does not convert agency decisionmaking into a scientific exercise). Of course, some scholars have argued that science itself represents little more than a contingent and negotiated consensus among participants. *See* Sheila Jasanoff, *What Judges Should Know About the Sociology of Science*, 32 JURIMETRICS J. 345, 347–49 (1992); Peter H. Schuck, *Multi-culturalism Redux: Science, Law, and Politics*, 11 YALE L. & POL'Y REV. 1, 16 (1993). *See generally* ALAN G. GROSS, THE RHETORIC OF SCIENCE (1990); KARIN D. KNORR-CETINA, THE MANUFACTURE OF KNOWLEDGE: AN ESSAY ON THE CONSTRUCTIVIST AND CONTEXTUAL NATURE OF SCIENCE (1981).

201. *See* Jonathan R. Macey, *The Transformation of the American Law Institute*, 61 GEO. WASH. L. REV. 1212, 1229–32 (1993) (defending the lobbying that occurred in connection with the ALI's *Corporate Governance* project); Alan Schwartz & Robert E. Scott, *The Political Economy of Private Legislatures*, 143 U. PA. L. REV. 595 (1995) (applying the insights of public choice theory to the ALI's activities); Symposium, *The American Law Institute: Process, Partisanship, and the Restatements of Law*, 26 HOFSTRA L. REV. 567 (1998); Symposium, *"From the Trenches and Towers": The Case for an In-Depth Study of the American Law Institute*, 23 LAW & SOC. INQUIRY 621 (1998).

202. *See* Lars Noah, *Pigeonholing Illness: Medical Diagnosis as a Legal Construct*, 50 HASTINGS L.J. 241, 293 (1999) ("As the significance of the[se] diagnostic manuals grows, groups with a stake in the outcome attempt to exert some influence, and the drafting process inevitably becomes more politicized and less driven by scientific expertise." (footnote omitted)); *see also id.* at 249–52, 287–96 (discussing the science of classifying diseases (nosology) and the social construction of illness).

203. *See* Anne-Marie Audet et al., *Medical Practice Guidelines: Current Activities and Future Directions*, 113 ANNALS INTERNAL MED. 709, 710–11 (1990); John Z. Ayanian et al., *Rating the Appropriateness of Coronary Angiography—Do Practicing Physicians Agree with an Expert Panel and with Each Other?*, 338 NEW ENG. J. MED. 1896, 1900 (1998); Arlene Fink et al., *Consensus Methods: Characteristics and Guidelines for Use*, 74 AM. J. PUB. HEALTH 979 (1984); Rolla Edward Park et al., *Physician Ratings of Appropriate Indications for Six Medical and Surgical Procedures*, 76 AM. J. PUB. HEALTH 766 (1986); Paul G. Shekelle et al., *The Reproducibility of a Method to Identify the Overuse and Underuse of Medical Procedures*, 338 NEW ENG. J. MED. 1888, 1888, 1893 (1998); Amiram Vinokur et al., *Group Decision Making by Experts: Field Study of Panels Evaluating Medical Technologies*, 49 J. PERSONAL. & SOC. PSYCHOL. 70 (1985); Steven H.

consensus may do no more than identify the point at which all the errors, oversimplifications, and biases converge; it does not necessarily identify what is best."[204]

Clinical practice guidelines may suffer from any number of shortcomings.[205] First, they "are constructed on a somewhat fragile data base."[206] Guidelines may replicate, if not magnify, all of the previously discussed limitations in the biomedical literature. Second, the process of developing guidelines, which some commentators have described as "haphazard,"[207] may itself introduce serious distortions.[208] Third, guidelines will do little good unless health care providers become aware of their existence. Their very multiplicity may "exacerbate the information deluge already cast upon the practicing physician."[209]

Woolf, *Practice Guidelines, a New Reality in Medicine: II. Methods of Developing Guidelines*, 152 ARCHIVES INTERNAL MED. 946 (1992).

204. Eddy, *Clinical Policies*, *supra* note 84, at 345; *see also* U.S. OFFICE OF TECH. ASSESSMENT, IDENTIFYING HEALTH TECHNOLOGIES THAT WORK: SEARCHING FOR EVIDENCE 164–66 (1994); Mark R. Chassin, *Standards of Care in Medicine*, 25 INQUIRY 437, 441 (1988); Charles E. Phelps, *The Methodologic Foundations of Studies of the Appropriateness of Medical Care*, 329 NEW ENG. J. MED. 1241, 1244 (1993) ("Methods based on reaching a consensus among experts do not create new scientific data, they only codify old beliefs."); Michael A. Webber, *Impact on the Pharmaceutical Industry of Changes in the American Health Care System: A Physician's Perspective*, 24 SETON HALL L. REV. 1260, 1311 (1994) ("Disagreements over the interpretations and validity of clinical trials, availability of long-term data for some drugs but not for others, conflicting assumptions about the negative as well as the positive attributes of drugs, contentious statistical questions, and difficulties measuring patient quality of life, all contributed to the angry but inconclusive published exchanges among experts" over a guideline for the prevention of congestive heart disease.); *cf.* Dennis S. O'Leary, Editorial, *The Need for Clinical Standards of Care*, 14 QUALITY REV. BULL. 31, 32 (1988) ("While consensus standards are inherently imperfect, they do reflect unique collections of wisdom and experience.").

205. *See* Steven H. Woolf et al., *Clinical Guidelines: Potential Benefits, Limitations, and Harms of Clinical Guidelines*, 318 BRIT. MED. J. 527, 529–30 (1999).

206. John D. Ayres, *The Use and Abuse of Medical Practice Guidelines*, 15 J. LEGAL MED. 421, 441 (1994); *see also id.* at 430–36, 442 ("The scientific studies and assumptions that merge in the development process may occasionally incorporate faulty or suspect data and inferences.").

207. *See id.* at 426 ("[S]tatistical manipulation, superficial analysis of the literature, and injudicious use of anecdotal information contributed to the weakness of this process." (footnotes omitted)).

208. *See id.* at 426–30, 442–43 ("Third-party users including courts, insurers, regulators, and policy makers should recognize the tenuous nature of parameter development and the substantial tensions tied to competing interests as these guidelines are constructed.").

209. *Id.* at 440 ("The number of parameters will certainly expand, creating even greater problems managing these additional pieces of data."); *see also id.* ("If the aim of these guidelines is to improve care and reduce costs, then the first order of business must be adequate dissemination to appropriate clinicians."); Clark C. Havighurst, *Practice Guidelines as Legal Standards Governing Physician Liability*, LAW & CONTEMP. PROBS., Spring 1991, at 87, 107 (defending pluralism among guidelines, but recognizing that "a multiplicity of inconsistent practice guidelines would present even more uncertainties for

Finally, adequate dissemination hardly ensures implementation.[210] Extensive research has shown that guidelines do not necessarily result in rapid or widespread modifications in practice patterns.[211]

Conflicts of interest may taint practice guidelines in much the same way as the underlying biomedical research literature. When specialty medical societies sponsor clinical practice guidelines, the financial interests of their members may influence the resolution of contested issues.[212] This explains the occasional, though

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physicians"); Jonathan Lomas et al., *Opinion Leaders vs. Audit and Feedback to Implement Practice Guidelines: Delivery After Previous Cesarean Section*, 265 JAMA 2202, 2206 (1991); Mary T. Koska, *Clinicians Struggle to Stay up to Date on Practice Parameters*, HOSPITALS, Dec. 5, 1991, at 38.

210. *See* Michael D. Cabana et al., *Why Don't Physicians Follow Clinical Practice Guidelines? A Framework for Improvement*, 282 JAMA 1458, 1461–63 (1999); Stuart J. Cohen et al., *The Impact of Reading on Physicians' Nonadherence to Recommended Standards of Medical Care*, 21 SOC. SCI. & MED. 909, 913 (1985); Lee Goldman, Editorial, *Changing Physicians' Behavior*, 322 NEW ENG. J. MED. 1524, 1525 (1990); Peter J. Greco & John M. Eisenberg, Editorial, *Changing Physicians' Practices*, 329 NEW ENG. J. MED. 1271, 1271 (1993); David E. Kanouse & Itzhak Jacoby, *When Does Information Change Practitioners' Behavior?*, 4 INT'L J. TECH. ASSESSMENT IN HEALTH CARE 27 (1988); Jonathan Lomas, *Words Without Actions? The Production, Dissemination, and Impact of Consensus Recommendations*, 12 ANN. REV. PUB. HEALTH 41, 55–60 (1991); Brian S. Mittman et al., *Implementing Clinical Practice Guidelines: Social Influence Strategies and Practitioner Behavior Change*, 18 QUALITY REV. BULL. 413, 421 (1992); *see also* Trinder, *supra* note 157, at 225 ("Implementing evidence-based practice will be a massive, lengthy and complex undertaking requiring much more than the simple provision of information and training in its appraisal.").

211. *See* Donald A. Brand et al., *Cardiologists' Practices Compared with Practice Guidelines: Use of Beta-Blockade After Acute Myocardial Infarction*, 26 J. AM. COL. CARDIOLOGY 1432, 1434–35 (1995) (finding less than a fifty percent compliance rate with guidelines calling for the use of beta-blockers after heart attack); Roberto Grilli & Jonathan Lomas, *Evaluating the Message: The Relationship Between Compliance Rate and the Subject of a Practice Guideline*, 32 MED. CARE 202, 206–07 (1994) (finding, based on a meta-analysis of 23 studies, an average compliance rate of almost fifty-five percent across 143 sets of guidelines); Antonio P. Legorreta et al., *Compliance with National Asthma Management Guidelines and Specialty Care*, 158 ARCHIVES INTERNAL MED. 457, 462–64 (1998); Jonathan Lomas et al., *Do Practice Guidelines Guide Practice? The Effect of a Consensus Statement on the Practice of Physicians*, 321 NEW ENG. J. MED. 1306, 1310 (1989); Steven H. Woolf, *Practice Guidelines: A New Reality in Medicine: III. Impact on Patient Care*, 153 ARCHIVES INTERNAL MED. 2646, 2648 (1993) (summarizing other studies that found similarly modest rates of adherence). *But cf.* Jeremy M. Grimshaw & Ian T. Russell, *Effect of Clinical Guidelines on Medical Practice: A Systematic Review of Rigorous Evaluations*, 342 LANCET 1317, 1321 (1993) (reporting that most studies "detected significant improvements in the process of care following the introduction of guidelines").

212. *See* GENERAL ACCOUNTING OFFICE, PRACTICE GUIDELINES: THE EXPERIENCE OF MEDICAL SPECIALTY SOCIETIES, PEMD 91-11, at 13–14 (1991) (explaining that one of several motivations for issuing guidelines is to respond to guidelines issued by another organization that are inimical to the interests of a medical society's members); Ayres, *supra* note 206, at 436–37; Clark C. Havighurst, *Practice Guidelines for Medical Care: The Policy Rationale*, 34 ST. LOUIS U. L.J. 777, 786, 789–90 n.35, 810 (1990); Rodwin, *supra*

so far unsuccessful, antitrust litigation against medical societies for the issuance of practice guidelines.[213] In some instances, insurance companies develop guidelines, which makes the potential conflict of interest even more apparent.[214] Health insurers may encounter less resistance if instead they endorse practice guidelines issued by respected medical organizations.[215]

It appears that pharmaceutical companies also have managed to affect the content of clinical practice guidelines in ways that give preference to the use of their products.[216] Even if they do not directly influence the formulation of guidelines, primary research funded by industry will do so,[217] and the disclosures of financial conflicts of interest in original journal articles will not reappear in the

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note 56, at 442; Woolf, *supra* note 211, at 2647 (explaining that groups sponsoring practice guidelines will have "different agendas," meaning, for instance, that "[g]uidelines developed by a specialty society with concerns about income-generating procedures performed by its members may differ from those of a multidisciplinary panel").

213. *See* Schachar v. Am. Acad. Ophthalmology, 870 F.2d 397 (7th Cir. 1989); Clark C. Havighurst, *Applying Antitrust Law to Collaboration in the Production of Information: The Case of Medical Technology Assessment*, LAW & CONTEMP. PROBS., Spring 1988, at 341, 357–60; Martin Rose & Robert F. Leibenluft, *Antitrust Implications of Medical Technology Assessment*, 314 NEW ENG. J. MED. 1490, 1492–93 (1986).

214. *See* Sara Rosenbaum et al., *Who Should Determine When Health Care Is Medically Necessary?*, 340 NEW ENG. J. MED. 229, 231 (1999); Barbara Martinez, *Care Guidelines by Insurers Face Scrutiny*, WALL ST. J., Sept. 14, 2000, at B1 (describing a new class action lawsuit attacking health insurers' reliance, when making decisions to deny coverage, on guidebooks produced by Milliman & Robertson Inc. that recommend very limited lengths of hospital stay); *see also* Quigley v. Jobe, 851 P.2d 236, 238 (Colo. Ct. App. 1992) (excluding insurer's risk management guidelines in a medical malpractice case); Colleen M. Grogan et al., *How Will We Use Clinical Guidelines? The Experience of Medicare Carriers*, 19 J. HEALTH POL. POL'Y & L. 7, 8 (1994) ("Costs, not quality medical care, are driving the federal government's push for guideline development."); Christine W. Parker, *Practice Guidelines and Private Insurers*, 23 J.L. MED. & ETHICS 57, 59–60 (1995).

215. *See* Milt Freudenheim, *Minnesota Health Plans to Standardize Treatments*, N.Y. TIMES, Mar. 13, 2001, at C1; Barbara Martinez, *Insurers Prepare to Fight Drug-Resistant Bacteria-With Reams of Data*, WALL ST. J., Apr. 9, 2001, at B1.

216. *See* Am. Med. Ass'n, *AMA Launches Clinical Practice Guideline Recognition Program to Evaluate Guidelines*, Press Release, July 16, 1997 (explaining that the AMA created this program as a "response to growing concerns among physicians about...the proliferation of proprietary guidelines of questionable scientific integrity, and the funding of guidelines by pharmaceutical firms that may preferentially suggest the use of their products") (quoted in Jodi M. Finder, *The Future of Practice Guidelines: Should They Constitute Conclusive Evidence of the Standard of Care?*, 10 HEALTH MATRIX 67, 90 (2000)); *see also* Edmund D. Pellegrino & Arnold S. Relman, *Professional Medical Associations: Ethical and Practical Guidelines*, 282 JAMA 984, 986 (1999) ("To avoid conflicts of interest, the professional medical association should not seek or accept support from companies that sell health care products or services."); David J. Rothman, *Medical Professionalism—Focusing on the Real Issues*, 342 NEW ENG. J. MED. 1284, 1285 (2000) (noting that pharmaceutical companies are major donors to specialty medical societies).

217. *See* Mariner, *supra* note 63, at 55; *see also* Crossen, *supra* note 151, at A1 (noting that an NIH guideline recommending antibiotic therapy for otitis media relied primarily on a study financed in part by interested drug companies).

secondary literature or practice guidelines that emerge from this research.[218] Similarly, if only positive results appear in the primary literature, whether because of a publication bias or pressure from sponsors, then guidelines may contain inappropriate recommendations.[219] One year ago, the government published new guidelines recommending–based on the completion of five large-scale RCTs demonstrating the utility of drugs called statins–more aggressive treatment of cholesterol,[220] leading to some suspicions about undue industry influence.[221]

Also like the biomedical literature, practice guidelines may quickly become outdated.[222] New research may render previously defensible guidelines obsolete—just think of the new views about hormone replacement therapy,[223] the treatment of peptic ulcers with antibiotics,[224] or revised recommendations for the

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218. *See* Robert Koepp & Steven H. Miles, Letter, *Meta-Analysis of Tacrine for Alzheimer Disease: The Influence of Industry Sponsors*, 281 JAMA 2287 (1999).

219. *See* Dan Vergano, *Drug Companies Send Unfavorable Research to the Nether Regions*, USA TODAY, May 17, 2001, at 8D (reporting that federal guidelines for the use of nicotine inhalers may have been skewed insofar as manufacturers prevented the publication of negative results, which researchers refer to as the "file drawer effect").

220. *See* Gina Kolata, *U.S. Panel Backs Broader Steps to Reduce Risk of Heart Attacks*, N.Y. TIMES, May 16, 2001, at A1 (reporting that the guideline "proposes nearly tripling the number of adults who should be taking cholesterol-lowering drugs"); *see also id.* (adding that the guidelines' sponsors were making special efforts to publicize them in order to encourage rapid implementation); David Brown, *More People Could Benefit from Statins, Study Finds*, WASH. POST, Nov. 14, 2001, at A2 (describing the results of a subsequent large-scale RCT confirming these results); Sally Squires, *NIH Revises Guidelines on Cholesterol*, WASH. POST, May 16, 2001, at A1 ("[A]t 200 pages, the scope of the guidelines may be daunting....'Are primary care physicians going to be just overwhelmed with the volume and detail here and not be able to act?'").

221. *See* Naomi Aoki, *U.S. Cholesterol Guidelines Have Some Suspecting Bias: Favorable Studies Said to Be Pharmaceutical Boosterism*, S.F. CHRON., June 4, 2001, at B4. Bristol-Myers Squibb, the manufacturer of Pravachol© (pravastatin sodium), took out a full-page advertisement in the *New York Times*, July 2, 2001, at A7, to draw attention to the new guidelines.

222. *See* Robert H. Fletcher & Suzanne W. Fletcher, Editorial, *Clinical Practice Guidelines*, 113 ANNALS INTERNAL MED. 645, 645–46 (1990); Mariner, *supra* note 63, at 56–57; Paul G. Shekelle et al., *Validity of the Agency for Healthcare Research and Quality Clinical Practice Guidelines: How Quickly Do Guidelines Become Outdated?*, 286 JAMA 1461, 1466 (2001) ("[H]alf of the guidelines became obsolete in 5.8 years."); *see also* INST. OF MED., GUIDELINES FOR CLINICAL PRACTICE, *supra* note 197, at 35, 45, 173–74 (emphasizing the need for regular updating).

223. *See* Okie, *supra* note 66, at A1 ("Healthy women should not take hormones after menopause to prevent heart disease,...according to new American Heart Association guidelines that represent a drastic change of the organization's recent advice."); *see also* Susan Parrott, *Heart Association Rewrites Guidelines: Wider Use of Drugs, Risk Control Urged*, SEATTLE TIMES, Sept. 25, 2001, at A11 (reporting on other revisions to the AHA guidelines).

224. *See* NIH Consensus Conference, Helicobacter pylori *in Peptic Ulcer Disease*, 272 JAMA 65, 68 (1994) ("The discovery of *H pylori* as a gastrointestinal pathogen [in the 1980s] has had a profound effect on current concepts of the pathogenesis of peptic ulcer disease.").

treatment of HIV.[225] After recommending the use of levodopa as the first-line therapy in treating Parkinson's disease for the last thirty-five years, neurologists recently revised a guideline to call for the initial use of dopamine antagonists instead.[226] Because of the consensus-building process involved in formulating guidelines, they may become obsolete more quickly than review articles and then prove to be more difficult to update.[227] Conversely, some commentators have objected that guidelines may have the effect of freezing the standard of care, thereby discouraging further research and innovation in areas about which the experts have reached a consensus.[228]

Finally, sponsoring organizations must resist the temptation to paper over the gaps or uncertainties in the biomedical literature. Although the utility of a practice guideline depends on the care and thoroughness of the literature review, many important questions will remain unanswered by the available biomedical research.[229] Overly prescriptive guidelines may incorrectly suggest definitive

225. *See* Nat'l Inst. of Allergy & Infectious Diseases, *HIV Treatment Guidelines Updated for Adults and Adolescents* (Feb. 4, 2001), *available at* http://www.niaid.nih.gov/newsroom/releases/hivguidelines.htm (last visited Apr. 1, 2002) (suggesting some delay before initiating drug therapy for HIV-infected patients).

226. *See* C. Warren Olanow et al., *An Algorithm (Decision Tree) for the Management of Parkinson's Disease (2001): Treatment Guidelines*, 56 NEUROLOGY S1, S27 (2001).

227. *See* Robert S.A. Hayward et al., *Users' Guides to the Medical Literature: VIII. How to Use Clinical Practice Guidelines: A. Are the Recommendations Valid?*, 274 JAMA 570, 573 (1995); Mark Kadzielski et al., *Peer Review and Practice Guidelines Under Health Care Reform*, 16 WHITTIER L. REV. 157, 162–63, 176 (1995) (noting concerns "that guidelines are going to be out of date before they are adopted").

228. *See* Robert L. Kane, *Creating Practice Guidelines: The Dangers of Overreliance on Expert Judgment*, 23 J.L. MED. & ETHICS 62, 63 (1995); William E. May, Editorial, *Consensus or Coercion*, 254 JAMA 1077 (1985); *see also* R. Dale Walker et al., *Medical Practice Guidelines*, 161 W.J. MED. 39, 43 (1994) ("[T]he contention that guidelines will discourage physicians from applying new technologies and interventions...should be empirically evaluated."); Susan Okie, *Analysis: Mammograms Don't Cut Cancer Death Risk*, WASH. POST, Oct. 19, 2001, at A2 (reporting that a systematic review of existing RCTs published by the Cochrane Collaboration found no evidence that mammography has value in screening for breast cancer, but adding that the conventional wisdom in favor of routine use in older women will make it nearly impossible to conduct a well-controlled, large-scale RCT designed to settle the question).

229. *See* David M. Eddy, *Guidelines for Policy Statements: The Explicit Approach*, 263 JAMA 2239, 2242 (1990); Arlene Fink et al., *Sufficiency of Clinical Literature on the Appropriate Uses of Six Medical and Surgical Procedures*, 147 W.J. MED. 609, 612–13 (1987); Gordon H. Guyatt et al., *Users' Guides to the Medical Literature: IX. A Method for Grading Health Care Recommendations*, 274 JAMA 1800, 1804 (1995); Lohr, *supra* note 196, at 53 (estimating that, "for perhaps 4 percent of all health services, the scientific evidence is strong; for perhaps 45 percent of patient care, the evidence is at best modest (although the level of consensus may be fairly robust); and for the other 51 percent, the evidence is very weak or nonexistent"); C. David Naylor, *Grey Zones of Clinical Practice: Some Limits to Evidence-Based Medicine*, 345 LANCET 840, 840–41 (1995). One of the early proponents of developing clinical practice guidelines suggested the use of a hierarchy of recommendations to reflect their strength, ranging from "standards" to

scientific support for a particular intervention and also fail to account for the inevitable need for flexibility in dealing with patient variability.[230] In addition, because of the essentially "trans-scientific" nature of guideline development,[231] users must understand the extent to which choices made in recommending appropriate treatments reflect value judgments.[232] One need only point to situations where practice guidelines deviate from one another in making recommendations for treating the same condition,[233] or where guidelines conflict

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"options," with "guidelines" falling in between these two extremes. *See* David M. Eddy, *Designing a Practice Policy: Standards, Guidelines, and Options*, 263 JAMA 3077 (1990).

230. *See* A. Gray Ellrodt et al., *Measuring and Improving Physician Compliance with Clinical Practice Guidelines: A Controlled Interventional Trial*, 122 ANNALS INTERNAL MED. 277, 280–81 (1995); Edward B. Hirshfeld, *Should Practice Parameters Be the Standard of Care in Malpractice Litigation?*, 266 JAMA 2886, 2888 (1991) ("Working with uncertainty is where medicine becomes an art as well as a science, and it is not feasible to expect practice parameters to capture and express the art of medicine."); Lars Noah, *Challenges in the Federal Regulation of Pain Management Technologies*, 30 J.L. MED. & ETHICS (forthcoming Dec. 2002) (discussing the significance of patient variability in response to opioids and other analgesic products).

231. *See* INST. OF MED., CLINICAL PRACTICE GUIDELINES, *supra* note 197, at 6 ("Conflicts in terminology and technique characterize the field; they are notable for the confusion they create and for what they reflect about differences in values, experiences, and interests among different parties."); Alexander Morgan Capron, *Practice Guidelines: How Good Are Medicine's New Recipes?*, 23 J.L. MED. & ETHICS 47, 48 (1995) (referring to "the value-laden nature of the topic"); Halpern, *supra* note 194, at 76–78; Pauly, *supra* note 140, at 68 ("[G]uidelines cannot be written based on medical knowledge alone, but must take measures of resource costs into account, as well as measures of value patients place on medical outcomes."); *cf.* Wendy E. Wagner, *The Science Charade in Toxic Risk Regulation*, 95 COLUM. L. REV. 1613, 1618–28, 1720–21 (1995) (describing risk assessment as a "trans-scientific" exercise because of the inevitable data gaps and uncertainties that require policy or value judgments on which science has little to offer).

232. *See* Andrew Farmer, *Medical Practice Guidelines: Lessons from the United States*, 307 BRIT. MED. J. 313, 313 (1993); Fred Gifford, *Outcomes Research and Practice Guidelines: Upstream Issues for Downstream Users*, HASTINGS CTR. REP., Mar.–Apr. 1996, at 38, 39, 43; Terrence M. Shaneyfelt et al., *Are Guidelines Following Guidelines? The Methodological Quality of Clinical Practice Guidelines in the Peer-Reviewed Medical Literature*, 281 JAMA 1900, 1904 (1999); Steven H. Woolf, *Do Clinical Practice Guidelines Define Good Medical Care?: The Need for Good Science and the Disclosure of Uncertainty When Defining 'Best Practices,'* 113 CHEST 166S, 167S (1998) ("Part of good science is clarifying where evidence ends and opinion begins.").

233. *See* David M. Eddy, *Resolving Conflicts in Practice Guidelines*, 264 JAMA 389, 389 (1990) (expressing concern that conflicting policies give "the impression that the medical profession does not have its act together"); Gene Feder, Letter, *Management of Mild Hypertension: Which Guidelines to Follow?*, 308 BRIT. MED. J. 470 (1994); Havighurst, *supra* note 209, at 113 ("The multiplicity of guidelines developed in a pluralistic environment would reflect not only differing assessments of the scientific evidence but also differing conclusions on the many trade-offs between benefits and costs."); Lockhart B. McGuire, *A Long Run for a Short Jump: Understanding Clinical Guidelines*, 113 ANNALS INTERNAL MED. 705, 705 (1990) ("It should not be surprising that guidelines emerging from different organizations often contain conflicting recommendations."); *see also* Ronald L. Goldman, *The Reliability of Peer Assessments of*

with research findings because of concerns about the expense of more effective therapies.[234]

Federal agencies play some role in the development and dissemination of practice guidelines. In 1989, Congress established the Agency for Health Care Policy and Research (AHCPR) in order to engage in outcomes research as well as to facilitate the creation and distribution of clinical practice guidelines.[235] The AHCPR—now redesignated as the Agency for Healthcare Research and Quality (AHRQ)—set up a dozen evidence-based practice centers to produce and disseminate reports that other organizations may use to establish practice guidelines.[236] In addition, responding to the sheer number and variety of practice

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Quality of Care, 267 JAMA 958, 958 (1992) ("Overall, physician agreement regarding quality of care is only slightly better than the level expected by chance. This finding casts considerable doubt on the standard practice of peer assessment...."); C. David Naylor, Editorial, *What Is Appropriate Care?*, 338 NEW ENG. J. MED. 1918, 1919–20 (1998) (explaining that differing opinions are unavoidable); Rolla Edward Park et al., *Physician Ratings of Appropriate Indications for Three Procedures*, 79 AM. J. PUB. HEALTH 445, 447 (1989). *But cf.* Paul G. Shekelle, Editorial, *Are Appropriateness Criteria Ready for Use in Clinical Practice?*, 344 NEW ENG. J. MED. 677, 678 (2001) ("There is demonstrably less variability in the development of appropriateness criteria than in the judgments of individual physicians....").

234. *See* Guyatt et al., *supra* note 35, at 1291 ("In both cases [TPA vs. streptokinase, and clopidogrel vs. aspirin], evidence from [RCTs] suggests the more expensive agents are, for many patients, more effective,...[but] many authoritative bodies recommended first-line treatment with the less effective drug, presumably because they believe society's resources would be better used in other ways."); *see also* David M. Eddy, *Applying Cost-Effectiveness Analysis: The Inside Story*, 268 JAMA 2575, 2581 (1992); Peter D. Jacobson & C. John Rosenquist, *The Use of Low-Osmolar Contrast Agents: Technological Change and Defensive Medicine*, 21 J. HEALTH POL., POL'Y & L. 243, 245–46, 258 (1996); J. Rosser Matthews, *Practice Guidelines and Tort Reform: The Legal System Confronts the Technocratic Wish*, 24 J. HEALTH POL., POL'Y & L. 275, 292–94 (1999) (explaining that guidelines which recommend diagnostic testing after a certain age reflect a trade-off between a statistically small benefit for younger patients and the social costs of routine screening); *Study Rates Colonoscopy as Far Superior Test*, N.Y. TIMES, Aug. 23, 2001, at A15.

235. *See* Omnibus Budget Reconciliation Act of 1989, Pub. L. No. 101–239, § 6103(a), 103 Stat. 2106, 2189–95 (codified as amended at 42 U.S.C. § 299b-1(a) (2000)) (directing the agency to "arrange for the development and periodic review and updating of-(1) clinically relevant guidelines that may be used by physicians, educators, and health care practitioners"); *see also* John M. Eisenberg, *Ten Lessons for Evidence-Based Technology Assessment*, 282 JAMA 1865, 1866–68 (1999); Charles Marwick, *Federal Agency Focuses on Outcomes Research*, 270 JAMA 164 (1993).

236. *See Evidence-Based Practice Centers*, *available at* http://www.ahrq.gov/clinic/epc (last visited Aug. 15, 2001); *see also* J. Jarrett Clinton, *Agency for Health Care Policy and Research: Overview of Purpose and Programs*, 49 FOOD & DRUG L.J. 449, 455–58 (1994) (describing the agency's initial success in "marketing" clinical practice guidelines); Eisenberg, *supra* note 41, at 378 (explaining that Congress recently directed the agency to "evaluate the rules of evidence that are used in evidence-based medicine"); Havighurst, *supra* note 212, at 804–19 (suggesting ways for the agency to facilitate pluralism in guideline development); *id.* at 795 ("Because it is

guidelines, AHCPR created an integrated database of existing guidelines.[237] Unlike some private organizations such as the AMA,[238] however, it does not purport to bestow any seal of approval. On the contrary, the agency includes a disclaimer to emphasize that it does not vouch for any of these guidelines.[239] In part, this hesitant stance grew from an incident in 1995, when Congress threatened to cut off AHCPR's funding after a vocal group of orthopedic surgeons complained about an agency report that had criticized the overuse of back surgery.[240]

For almost a quarter of a century, the National Institutes of Health (NIH) have held conferences and generated "consensus statements" that may serve as clinical practice guidelines.[241] In some cases, the NIH has undertaken such efforts

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extraordinarily difficult for anyone, let alone a busy practicing physician, to synthesize the teachings of numerous, usually conflicting studies of uncertain scientific validity into a reliable basis for each clinical decision, a public investment in such syntheses could pay substantial social dividends.").

237. *See* 63 Fed. Reg. 18,027 (Apr. 13, 1998); Linda O. Prager, *Internet-Based Guideline Repository Unveiled*, AM. MED. NEWS, Feb. 1, 1999, at 1; *see also* Barry R. Furrow, *Broadcasting Clinical Guidelines on the Internet: Will Physicians Tune In?*, 25 AM. J.L. & MED. 403, 419–21 (1999) (extolling the promise of this and similar commercial databases); Susan Okie, *Reform Health Care, Study Urges*, WASH. POST, Mar. 2, 2001, at A2 (describing a new IOM report that called on Congress to provide increased funding for AHRQ for guideline development and dissemination).

238. *See AMA Panel on Guidelines Sorts Good from Misguided*, AM. MED. NEWS, Jan. 10, 1994, at 1.

239. *See National Guideline Clearinghouse*, *available at* http://www.guideline.gov/index.asp (last visited Aug. 15, 2001) (refusing to make any "warranties concerning the content or clinical efficacy of the clinical practice guidelines," and adding that "[i]nclusion of any guideline in the NGC does not constitute or imply an endorsement by the AHRQ"). Some commentators have argued that the agency should play a central role in certifying guidelines. *See* Rosoff, *supra* note 198, at 355–66 (focusing on certification as a mechanism for facilitating their application in litigation); *see also* Lucian L. Leape, Editorial, *Translating Medical Science into Medical Practice: Do We Need a National Medical Standards Board?*, 273 JAMA 1534, 1535–36 (1995) (proposing mandatory compliance with some guidelines as a response to low rates of voluntary adherence); Seymour Perry & Mae Thamer, *Medical Innovation and the Critical Role of Health Technology Assessment*, 282 JAMA 1869, 1870–72 (1999).

240. *See* Neil A. Lewis, *Agency's Report Provokes a Revolt*, N.Y. TIMES, Sept. 14, 1995, at A16; *see also* John Frank, *The Nonsurgical Management of Acute Low Back Pain: Cutting Through the AHCPR Guidelines*, 339 NEW ENG. J. MED. 484, 484 (1998) (book review) ("After a coordinated attack on the agency by those who disagreed with its findings, many of whom had vested interests in procedures found by the panel to have no evidentiary basis, the AHCPR got out of the guidelines-producing business in 1996.").

241. *See* Itzhak Jacoby, Editorial, *Evidence and Consensus*, 259 JAMA 3039 (1988); Seymour Perry, *The NIH Consensus Development Program: A Decade Later*, 317 NEW ENG. J. MED. 485, 486–87 (1987). The program has attracted its share of criticism. *See* Gerald E. Markle & Daryl E. Chubin, *Consensus Development in Biomedicine: The Liver Transplant Controversy*, 65 MILBANK Q. 1, 21 (1987) ("[T]he [consensus development] program aims not so much to resolve the legitimate ambiguities of science, but rather to authorize a political settlement of scientific differences."); Drummond Rennie, Editorial, *Consensus Statements*, 304 NEW ENG. J. MED. 665, 666 (1981) (complaining that the

when privately developed guidelines provided inconsistent or controversial recommendations.[242] As happens with practice guidelines issued by private entities, these authoritative pronouncements do not always catch on quickly.[243] NIH also may issue "clinical alerts" designed to notify physicians of important new findings from large-scale RCTs.[244] The Centers for Disease Control and Prevention (CDC) also sometimes issue practice guidelines and engage in outreach activities designed to educate health care providers and patients.[245] One of their successful recent initiatives sought to discourage the overprescribing of antibiotics.[246]

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resulting recommendations are "bland generalities that represent the lowest common denominator of a debate—the only points on which the experts could wholeheartedly agree—and that these points must be so mild, so far from the cutting edge of progress, and so well established that surely everyone must already know them"); Paul M. Wortman et al., *Do Consensus Conferences Work? A Process Evaluation of the NIH Consensus Development Program*, 13 J. HEALTH POL., POL'Y & L. 469, 489–95 (1988) (identifying a variety of flaws in the process).

242. For instance, the NIH recently issued a consensus statement on the use of adjuvant therapies in treating breast cancer patients. *See Panel Backs Combination of Breast Cancer Drugs*, WASH. POST, Nov. 4, 2000, at A8.

243. *See* Jacqueline Kosecoff et al., *Effects of the National Institutes of Health Consensus Development Program on Physician Practice*, 258 JAMA 2708, 2712 (1987) (reviewing eleven guidelines issued by the NIH, and finding an average adherence rate of fifty-seven percent after three years); Hilary Macht Felgran, *Mastectomies, Sometimes Unneeded, Prevail*, N.Y. TIMES, Jan. 23, 2001, at D7 ("Nearly 10 years after an expert panel convened by the National Institutes of Health declared breast-conserving surgery the preferred treatment for most women with early-stage cancer, on average about half of those eligible for the procedure continue to undergo full mastectomies," which may result in part from the inertia of physicians trained in an earlier era.).

244. *See* Bernadine Healy, *Issuing Clinical Alerts*, 269 JAMA 3096 (1993); *see also* Cary P. Gross et al., *Relation Between Prepublication Release of Clinical Trial Results and the Practice of Carotid Endarterectomy*, 284 JAMA 2886, 2890–92 (2000) (finding that a pair of NIH alerts had a prompt impact on the use of a controversial procedure, but cautioning that physicians may have overreacted to the information by disregarding some of the caveats about the underlying RCTs); Robert L. Kane & Judith Garrard, Editorial, *Changing Physician Prescribing Practices: Regulation vs. Education*, 271 JAMA 393, 394 (1994); Robert E. Wittes, *Of Clinical Alerts and Peer Review*, 80 J. NAT'L CANCER INST. 984, 985 (1988) (recognizing that this "constitutes an admittedly unorthodox mechanism that bypasses the usual process of peer review").

245. *See* ELIZABETH W. ETHERIDGE, SENTINEL FOR HEALTH: A HISTORY OF THE CENTERS FOR DISEASE CONTROL 296–98, 305–06, 343 (1992).

246. *See* Anita Manning, *Doctors Are Slowing Use of Antibiotics for Children*, USA TODAY, Sept. 11, 2000, at 6D; *see also* Ralph Gonzales et al., *Principles of Appropriate Antibiotic Use for Treatment of Acute Respiratory Tract Infections in Adults: Background, Specific Aims, and Methods*, 134 ANNALS INTERNAL MED. 479, 481–82 (2001) (introducing a series of CDC guidelines calling for restraint in prescribing antibiotics for adults).

D. Industry Advertising

Companies that sell health care technologies play an important role in the transmission of biomedical knowledge. Apart from the previously mentioned incentives to generate research, they also have the resources to communicate valuable information to health care professionals,[247] but, not surprisingly, these companies have promotional rather than purely educational goals in mind.[248] As other sources of funding for physician education have become scarce, industry support becomes both more critical and potentially subject to abuse.[249] For instance, increasing drug company sponsorship of CME programs has raised concerns that these events represent primarily promotional as opposed to educational events.[250] In addition, one review of pharmaceutical advertisements

247. *See* J. Howard Beales III, *Economic Analysis and the Regulation of Pharmaceutical Advertising*, 24 SETON HALL L. REV. 1370, 1394, 1397–98 (1994); John F. Beary III, Editorial, *Pharmaceutical Marketing Has Real and Proven Value: Characteristics of Materials Distributed by Drug Companies*, 11 J. GEN. INTERNAL MED. 635, 635–36 (1996); Alan F. Holmer, *Industry Strongly Supports Continuing Medical Education*, 285 JAMA 2012, 2012 (2001); Keith B. Leffler, *Persuasion or Information? The Economics of Prescription Drug Advertising*, 24 J.L. & ECON. 45, 74 (1981) (concluding "that product promotion has a significant positive effect on the entry success of therapeutically important new drugs"); Susan Heilbronner Fisher, Note, *The Economic Wisdom of Regulating Pharmaceutical "Freebies,"* 1991 DUKE L.J. 206, 225–28, 239 ("[D]etailing serves an important informational purpose of making doctors aware of the newest technologies on the market. This helps physicians make more informed prescribing decisions....").

248. *See* Allen F. Shaughnessy et al., *Separating the Wheat from the Chaff: Identifying Fallacies in Pharmaceutical Promotion*, 9 J. GEN. INTERNAL MED. 563, 566–67 (1994); Daniel Stryer & Lisa A. Bero, *Characteristics of Materials Distributed by Drug Companies: An Evaluation of Appropriateness*, 11 J. GEN. INTERNAL MED. 575, 579 (1996).

249. *See* Robert M. Tenery, Jr., *Interactions Between Physicians and the Health Care Technology Industry*, 283 JAMA 391, 392 (2000) ("Unfortunately, while the need for CME for physicians has increased with rapidly expanding technology, the funding from independent sources has decreased proportionately."); Dan Vergano, *Who's Teaching the Doctors? Drug Firms Sponsor Required Courses—and See Their Sales Rise*, USA TODAY, Mar. 9, 2000, at D1.

250. *See* Nina A. Bickell, *Drug Companies and Continuing Education*, 10 J. GEN. INTERNAL MED. 392 (1995); David A. Kessler, *Drug Promotion and Scientific Exchange*, 325 NEW ENG. J. MED. 201, 201 (1991); Arnold S. Relman, *Separating Continuing Medical Education from Pharmaceutical Marketing*, 285 JAMA 2009, 2009–11 (2001); Chris Adams, *FDA Cites Firms for Improper Statements*, WALL ST. J., July 30, 2001, at B6; Gina Kolata, *Where Marketing and Medicine Meet*, N.Y. TIMES, Feb. 10, 1998, at A14 (reporting one cardiologist's description of a lavish conference indirectly funded by the industry as "one big infomercial"). Even the naming of clinical trials with memorable acronyms (e.g., GUSTO) has been criticized as a subtle form of advertising that may mislead researchers and subjects about the effectiveness of the investigational treatment. *See* Michael Berkwits, *Clinical Trial Acronyms and the "Branding" of Clinical Research*, 133 ANNALS INTERNAL MED. 755, 757–59 (2000).

appearing in medical journals found significant discrepancies in the information provided.[251]

Whether presented at a symposium, in print advertising, or during a sales visit, exaggerated promotional claims would raise no serious concerns if physicians routinely discounted them, but research indicates that advertising does influence prescribing behavior.[252] Drug "detailing," which refers to office visits by sales representatives, dates back to 1850, and it remains an important promotional mechanism.[253] While the payola-style abuses of earlier decades have largely vanished, sales strategies have become more sophisticated, allowing companies to target particular health care professionals by using databases that track prescribing behavior, and detail representatives continue to "wine and dine" physicians.[254]

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251. *See* Michael S. Wilkes et al., *Pharmaceutical Advertisements in Leading Medical Journals: Experts' Assessments*, 116 ANNALS INTERNAL MED. 912, 918 (1992) ("The finding of problems in a large proportion of pharmaceutical advertisements is troublesome, given research suggesting that drug advertising serves as a major source of information for practicing physicians."). The study's suggestion that ninety-two percent of the advertisements violated FDA requirements, *see id.* at 917, drew deserved criticism. *See* J. Howard Beales III & William C. MacLeod, *Assessments of Pharmaceutical Advertisements: A Critical Analysis of the Criticism*, 50 FOOD & DRUG L.J. 415, 443 (1995); Paul H. Rubin, *Are Pharmaceutical Ads Deceptive?*, 49 FOOD & DRUG L.J. 7, 10–11 (1994). Even so, the finding that many advertisements provided incomplete information undermines claims about their educational value. Studies have found similar problems in pitches made by salespersons during visits to health care providers. *See* Michael G. Ziegler et al., *The Accuracy of Drug Information from Pharmaceutical Representatives*, 273 JAMA 1296, 1297–98 (1995).

252. *See* Jerry Avorn et al., *Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, 73 AM. J. MED. 4, 8 (1982) (concluding that "the predominance of nonscientific rather than scientific sources of drug information is consistent with what would be predicted from communications theory and marketing research data"); Marilyn Y. Peay & Edmund R. Peay, *Differences Among Practitioners in Patterns of Preference for Information Sources in the Adoption of New Drugs*, 18 SOC. SCI. & MED. 1019, 1024 (1984) (finding that physicians in Australia initially placed greater reliance on information about new drugs from salespersons than from colleagues or journal articles). For a somewhat contrary finding, see John I. Mackowiak & Jean Paul Gagnon, *Effects of Promotion on Pharmaceutical Demand*, 20 SOC. SCI. & MED. 1191, 1194–96 (1985).

253. *See* Abigail Zuger, *Fever Pitch: Getting Doctors to Prescribe Is Big Business*, N.Y. TIMES, Jan. 11, 1999, at A1 ("[T]he pharmaceutical sales force has exploded, from about 35,000 full-time sales representatives and supervisors in the top 40 pharmaceutical companies in 1994 to more than 56,000 in 1998....That translates into nearly one drug salesperson and almost $100,000 for every 11 practicing physicians in the United States...."); *see also* 65 Fed. Reg. 81,082, 81,108 (Dec. 22, 2000) (estimating that "23.7 million office and hospital calls per year [are] made by pharmaceutical representatives"); Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 FOOD & DRUG L.J. 309, 309–16 (1992).

254. *See* Chris Adams, *Doctors on the Run Can 'dine 'n' Dash" in Style in New Orleans*, WALL ST. J., May 14, 2001, at A1; Bill Brubaker, *Drug Firms Still Lavish Pricey Gifts on Doctors*, WASH. POST, Jan. 19, 2002, at E1; Sheryl Gay Stolberg & Jeff Gerth,

Although most doctors express probably unjustified confidence that such sales pitches and freebies do not influence their own prescribing behavior, they do worry about their more gullible colleagues.[255]

Apparently no one is entirely immune. One recent review of studies about promotional interactions between physicians and the pharmaceutical industry reached the following conclusion:

> [M]ost studies found negative outcomes associated with the interaction. These included an impact on knowledge (inability to identify wrong claims about medication), attitude (positive attitude toward pharmaceutical representatives; awareness, preference, and rapid prescription of a new drug), and behavior (making formulary requests for medications that rarely held important advantages over existing ones; nonrational prescribing behavior; increasing prescription rate; prescribing fewer generic but more expensive, newer medications at no demonstrated advantage).[256]

Advertising also may result in the selection of a therapeutic intervention in seeming disregard of evidence questioning its utility.[257] (Conversely, newly

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High-Tech Stealth Being Used to Sway Doctor Prescriptions, N.Y. TIMES, Nov. 16, 2000, at A1 (noting the industry's justification that "physicians are hungry for information about" new drugs); *see also* Council on Ethical & Judicial Aff., AMA, *Guidelines on Gifts to Physicians from Industry: An Update*, 56 FOOD & DRUG L.J. 27, 28 (2001) ("[T]he AMA is about to embark on a nationwide campaign to educate physicians about the importance of reducing and eliminating inappropriate gifts from industry."); Thomas N. Bulleit, Jr. & Joan H. Krause, *Kickbacks, Courtesies, or Cost-Effectiveness?: Application of the Medicare Antikickback Law to the Marketing and Promotional Practices of Drug and Medical Device Manufacturers*, 54 FOOD & DRUG L.J. 279, 296–309 (1999); Susan Okie, *AMA Criticized for Letting Drug Firms Pay for Ethics Campaign*, WASH. POST, Aug. 30, 2001, at A3.

255. *See* Michael A. Steinman et al., *Of Principles and Pens: Attitudes and Practices of Medicine Housestaff Toward Pharmaceutical Industry Promotions*, 110 AM. J. MED. 551, 555–56 (2001); *see also* W. Paul McKinney et al., *Attitudes of Internal Medicine Faculty and Residents Toward Professional Interaction with Pharmaceutical Sales Representatives*, 264 JAMA 1693, 1696 (1990) ("Few faculty members and residents perceived an influence of PRs on their own decision making....").

256. Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 JAMA 373, 378 (2000); *see also* Mary-Margaret Chren et al., *Doctors, Drug Companies, and Gifts*, 262 JAMA 3448, 3449 (1989); Jerome P. Kassirer, *Financial Indigestion*, 284 JAMA 2156, 2157 (2000); Zuger, *supra* note 253, at A1 ("[S]tudies have repeatedly shown that doctors who say they rely a great deal on information supplied by pharmaceutical representatives instead of medical journals tend to have more expensive prescribing habits than other doctors, and are somewhat less likely to choose the best drugs for a given job."); *id.* (adding that, "[f]or some doctors, keeping an open door for the sales representatives is an educational imperative made more essential by the glut of new products").

257. *See* Teri A. Manolio et al., *Trends in Pharmacologic Management of Hypertension in the United States*, 155 ARCHIVES INTERNAL MED. 829, 836 (1995) (describing dramatic increases in the use of calcium antagonists and ACE inhibitors notwithstanding weak evidence of superior effectiveness in the routine treatment of

discovered uses of approved drugs reported in the scientific literature may catch on more slowly because historically the FDA prohibited companies from advertising such "off-label" uses.[258] Indeed, the time that it normally takes before physicians become aware of newly reported information represents one of the primary rationales for now allowing drug manufacturers to disseminate reprints of articles that discuss such uses.[259]) By equiping them with critical appraisal skills, EBM may encourage practitioners to adopt a more skeptical stance when exposed to promotional materials.[260]

Finally, pharmaceutical companies increasingly target their advertising directly at patients, whether in print, on television, or through the Internet.[261] In particular, the Internet has provided lay persons with access to a wealth of information previously available only to medical professionals. Whether or not pharmaceutical companies sponsor these web sites, a good deal of the information is incomplete or inaccurate.[262] Although they generally lack the expertise to

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hypertension as compared with older (and cheaper) antihypertensive drugs); Marvin Moser, *Why Are Physicians Not Prescribing Diuretics More Frequently in the Management of Hypertension?*, 279 JAMA 1813, 1813 (1998) ("Reasons include extensive promotion of other medications at medical meetings and medical journals...."); David Siegel & Julio Lopez, *Trends in Antihypertensive Drug Use in the United States: Do the JNC V Recommendations Affect Prescribing?*, 278 JAMA 1745, 1747 (1997) (noting that expert recommendations did not substantially alter the choice of drug treatment for hypertensive patients, and speculating that advertising for newer antihypertensive agents helped account for this pattern); Denise Grady, *As Silent Killer Returns, Doctors Rethink Tactics to Lower Blood Pressure*, N.Y. TIMES, July 14, 1998, at F1; *see also* Rita Rubin, *Taking on a Drug Giant: Two Patients File Suit Against Pfizer*, USA TODAY, May 23, 2001, at 1D (describing one manufacturer's successful efforts at damage control after a large-scale RCT found that its drug Cardura created a greater risk of serious cardiac side effects than diuretics).

258. *See infra* Part IV.A.2.

259. *See* Beales, *supra* note 247, at 1370, 1392, 1394–96.

260. *See* Lipman, *supra* note 197, at 59.

261. *See* Julie Appleby, *Prescriptions Increase as Drugmakers Spend More on Ads*, USA TODAY, Feb. 21, 2001, at 6B (reporting that companies spent more than $2 billion advertising prescription drugs directly to consumers in 2000, and that sales increased to $145 billion); Gardiner Harris, *Drug Firms, Stymied in the Lab, Become Marketing Machines*, WALL ST. J., July 6, 2000, at A1 ("Since 1993, when television advertising of prescription drugs became common in the U.S., sales of them have doubled, to $101 billion in 1999."); *see also* Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141, 148–51 (1997).

262. *See* Gretchen K. Berland et al., *Health Information on the Internet: Accessibility, Quality, and Readability in English and Spanish*, 285 JAMA 2612, 2619–20 (2001); Piero Impicciatore et al., *Reliability of Health Information for the Public on the World Wide Web: Systematic Survey of Advice on Managing Fever in Children at Home*, 314 BRIT. MED. J. 1875, 1878 (1997); Alejandro R. Jadad & Anna Gagliardi, *Rating Health Information on the Internet: Navigating to Knowledge or to Babel?*, 279 JAMA 611, 613–14 (1998); Sandra G. Boodman, *Medical Web Sites Can Steer You Wrong*, WASH. POST, Aug. 10, 1999, at Z7; *see also* Laura Landro, *People Power*, WALL ST. J., Feb. 21, 2001, at R8 (describing efforts to make MEDLINE and other government sites more user friendly for lay persons).

understand much of this information, many patients have the time and motivation to seek it out, and then they may confront their physicians with such research.[263] Undoubtedly, many health care professionals will regard this behavior as unsettling,[264] but, wholly apart from the possible benefits of empowering patients, some physicians may come to welcome such initiative as providing them with an additional method for accessing the relevant literature.[265] After all, if physicians regard pharmaceutical company sales representatives as a useful conduit for information, why should they resist when patients convey it?

IV. THE ROLES PLAYED BY LEGAL INSTITUTIONS

So far, this Article has summarized the basic categories of biomedical information (personal experience, observational studies, and RCTs) as well as the mechanisms used for its dissemination (conferences, journals, textbooks, practice guidelines, and advertising), highlighting important shortcomings along the way. Proponents of EBM urge physicians to prefer RCTs and to look for them in systematic compilations of the primary literature, but physicians continue to give greater credence to anecdotal information and, whether they admit it or not, may depend on advertising for additional guidance. Indeed, all of the sources for biomedical information may have become corrupted to a greater or lesser extent by promotional efforts,[266] a concern that proponents of EBM seem to have overlooked altogether.

Legal institutions may play various roles in this process. The preceding section already mentioned that three units of the Public Health Service (PHS)—namely, AHCPR/AHRQ, NIH, and CDC—have facilitated outcomes research, guideline development, and dissemination. The FDA, another unit within the PHS, plays a more aggressive role in its capacity as a regulatory agency concerned with supervising the commercialization of medical technologies. The courts also may influence the production and dissemination of biomedical knowledge, through

263. *See* Goldsmith, *supra* note 134, at 152 ("Into this expanding knowledge vacuum charges the cyber-assisted patient...[who now has] access to the same scientific databases, clinical trials listings, new drug information, and other sources that their own physicians often do not have time to analyze carefully....").

264. *See* Nancy Ann Jeffrey, *A Little Knowledge: Doctors Are Suddenly Swamped with Patients Who Think They Know a Lot More Than They Actually Do*, WALL ST. J., Oct. 19, 1998, at R8.

265. *See* Goldsmith, *supra* note 134, at 152 ("The idea that physicians should rely on patients to update them on developments in their own field is a stunning reversal of the traditional information flow in medicine. Yet physicians may come to discover that some of their patients are reliable bridges to emerging medical knowledge.").

266. *Cf.* Proctor v. Davis, 682 N.E.2d 1203, 1208–09 (Ill. App. Ct. 1997) ("The practice of publicizing unapproved uses of drugs, when sponsored by the pharmaceutical company, is not approved by the FDA....These writings, of course, would be addressed to the medical community and become available to ophthalmologists, thereby becoming, incredibly, part of the current medical literature...."); *id.* at 1215 ("Although it is assumed that physicians will keep abreast of current medical literature, here, part of the flawed literature was generated by Upjohn.").

both products liability and medical malpractice litigation. These different forces are taken up in turn below.

A. FDA Regulation

The Food and Drug Administration plays a central role in supervising the production and dissemination of information concerning medical technologies.[267] The FDA mandates that detailed "package inserts" accompany these products, often dictating the precise content of such labeling.[268] (Oddly enough, notwithstanding the clear rigor of this process, proponents of EBM never mention package inserts as a valuable source of evidence-based recommendations for practitioners.) In addition, the agency carefully monitors the advertising of medical technologies, which better coincides with the reality that promotional messages–rather than EBM's idealized vision of using the best available research–strongly influence clinical decisionmaking.

Before marketing a new drug or medical device, a company must persuade the FDA of the product's safety and effectiveness, which normally requires the submission of results from controlled clinical trials.[269] This comports with the statute's legislative history, which "show[ed] a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous."[270] Indeed, after Congress amended the statute in 1962 to add proof of

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267. *See* LARS NOAH & BARBARA A. NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS ch. 3–4 (Foundation Press forthcoming May 2002). Although all medical technologies are information-laden, in some instances the regulated product is almost exclusively informational. *See* Vincent Brannigan, *The Regulation of Medical Expert Computer Software as a "Device" Under the Food, Drug, and Cosmetic Act*, 27 JURIMETRICS J. 370, 373–78 (1987) (questioning the FDA's assertion of jurisdiction over medical software); Frank D. Nguyen, Comment, *Regulation of Medical Expert Systems: A Necessary Evil?*, 34 SANTA CLARA L. REV. 1187, 1208–11, 1230–32 (1994) (proposing alternatives to FDA regulation of software as a medical device); *see also* Dereck L. Hunt et al., *Effects of Computer-Based Clinical Decision Support Systems on Physician Performance and Patient Outcomes: A Systematic Review*, 280 JAMA 1339, 1334–35 (1998) ("[T]he increasing number and quality of CDSS trials in the past few years and the rapid assimilation of technological information into clinical settings bode well for the future of improving the effectiveness and efficiency of medical care.").

268. *See* 21 C.F.R. §§ 201.56–.57 (drugs), 801.109(c) (medical devices) (2001).

269. *See id.* § 314.126(e) (providing that, in reviewing an application for new drug approval, the agency will not consider "[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation").

270. Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 619 (1973); *see also id.* at 630 ("[C]linical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy."). Several academic scientists who testified before Congress in support of imposing a proof of effectiveness requirement emphasized the unreliability of impressionistic judgments about drug efficacy made by individual physicians. *See Hearings on S. 1552 Before the Subcomm. on Antitrust & Monopoly of the Sen. Judiciary Comm.*, 87th Cong. 269 (1961) (testimony of Dr. William Bean, Iowa St. Univ.); *id.* at 430 (testimony of Dr. Maxwell Finland, Harvard); *id.* at 283 (testimony of Dr. Louis Lasagna, Johns Hopkins) ("The history of medicine is,

effectiveness as a prerequisite for market approval, a retrospective review conducted by the National Academy of Sciences found that more than half of the claims for drugs then on the market probably could not satisfy this new statutory requirement.[271] In enacting the statute, Congress also sought to ensure that physicians would get ready access to reliable information about pharmaceutical products.[272]

1. Labeling Requirements

The FDA strictly regulates the labeling that accompanies medical technologies,[273] jealously controlling the information communicated to health professionals. Nonetheless, it has recognized that labeling should not provide the sole source of information relevant to utilization decisions. In part, this grows from the inevitable obsolescence of the labeling as well as the variable appropriate uses to which physicians may put approved products. In addition, it reflects an assumption that health care professionals would inform themselves by consulting other sources of drug information. In the course of rejecting suggestions that labels communicate dissenting scientific views, the agency emphasized that "labeling is not intended to be a dispositive treatise of all possible medical opinion.... The opinions of individual physicians on such matters can be, and are, thoroughly and adequately discussed through medical journals, treatises, meetings of professional

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unhappily, replete with examples of useless drugs employed for years, decades, or centuries, by countless physicians before a few properly conducted experiments proved the drugs to be without value."); Pharm. Mfrs. Ass'n v. Richardson, 318 F. Supp. 301, 307 (D. Del. 1970) (recounting other similar testimony at the congressional hearings).

271. *See* Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 210 n.160 (1971). A similar technology assessment effort undertaken by the executive branch in the late 1970s concluded that forty percent of seventy-five technologies reviewed for purposes of Medicare reimbursement were unproven or ineffective. *See* Seymour Perry, *The Brief Life of the Center for Health Care Technology*, 307 NEW ENG. J. MED. 1095, 1097–98 (1982); *see also* Maxwell J. Mehlman, *Health Care Cost Containment and Medical Technology: A Critique of Waste Theory*, 36 CASE W. RES. L. REV. 778, 786 (1986) ("Medical history reveals a number of technologies that flourished for a time but that were eventually determined to be ineffective."); Temple, *supra* note 114, at 1902 ("Without evidence we are back in the past, where bleeding, purging and heaven knows what else, all supported by expert opinion and elaborate rationales, were the standard treatments....").

272. *See* S. REP. NO. 87-1744, at 37 (1962) (separate views of Sen. Kefauver et al.), *reprinted in* 1962 U.S.C.C.A.N. 2884, 2902 ("Leading physicians testified that it is impossible to keep currently informed of the state of medical knowledge to be found scattered in hundreds of medical journals on the 400 new drugs introduced each year."); Upjohn Co. v. Finch, 422 F.2d 944, 953–54 (6th Cir. 1970).

273. *See* 21 C.F.R. § 201.57(d)–(g) (requiring substantiation for inclusion of risk information in labeling); 44 Fed. Reg. 37,434, 37,447 (June 26, 1979) (explaining that to "includ[e] theoretical hazards as contraindications in drug labeling would cause that very important section of the labeling to lose its significance"); *id.* at 37,453 (providing that even the "Adverse Reactions" section of a package insert "would not include unsubstantiated reactions").

associations, and other similar events."[274] Thus, the FDA originally regarded the package insert as a supplement to the regular channels of information that physicians normally consulted.

Even more fundamentally, the agency's concession that drug labeling should not provide the sole source of prescribing information recognized that too much information can be a bad thing. In issuing a rule governing the format of package inserts, the FDA rejected suggestions calling for the inclusion of general statements about good professional practice: "There are potentially many such statements, which, if all are included in drug labeling, would transform labeling into small textbooks of medicine."[275] As explained in the preamble to the proposed regulation, the agency hoped to improve package inserts in part by "eliminating extraneous information which can best be obtained from the published literature."[276]

Nonetheless, package inserts clearly now include recommendations about appropriate prescribing. For instance, the FDA recently proposed mandating a best practices statement in the labeling of antibiotics, reminding physicians against overprescribing because of the public health consequences associated with growing drug-resistance.[277] In addition, "Contraindication" statements recommend against any use in particular types of patients. Although the agency generally does not make comparative safety and effectiveness judgments when deciding whether to approve a new drug or medical device,[278] and it has resisted suggestions that it review comparative effectiveness claims for inclusion in product labeling or advertising, in some instances the FDA has approved statements indicating that a product is the "drug of choice" or "first line" therapy (or vice-versa).[279] The agency

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274. 40 Fed. Reg. 28,582, 28,583 (July 7, 1975). The regulation prohibits the inclusion of dissenting views to accompany FDA-mandated warning statements. *See* 21 C.F.R. § 1.21(c)(1) (2001). As explained in the preamble to the proposed regulation, the agency feared that including disclamatory opinions in warnings would "be confusing and misleading." 39 Fed. Reg. 33,229, 33,232 (Sept. 16, 1974); *see also id.* at 33,231 (adding that "disagreement is properly the subject of scientific discussion in professional journals and symposia, but not in drug labeling").

275. 44 Fed. Reg. 37,434, 37,436 (June 26, 1979) ("Physicians are always in a position to pursue additional information through normal educational sources, such as treatises and medical journals.").

276. 40 Fed. Reg. 15,392, 15,392 (Apr. 7, 1975); *see also id.* at 15,394 ("The Commissioner clearly recognizes that the labeling of a marketed drug does not always contain all the most current information available to physicians relating to the proper use of the drug in good medical practice. Advances in medical knowledge and practice inevitably precede labeling revision....").

277. *See* 65 Fed. Reg. 56,511, 56,518 (Sept. 19, 2000); *see also* 65 Fed. Reg. 81,082, 81,095 (Dec. 22, 2000) (proposing revisions in the content of prescription drug labeling to reduce the tendency to overprescribe antibiotics).

278. *See* Elhauge, *supra* note 90, at 1593; Mehlman, *supra* note 271, at 788 (explaining that the FDA "has occasionally, albeit rarely, denied approval to market a drug on the basis that it was less safe or less effective than an alternative already on the market").

279. *See* Temple, *supra* note 114, at 1888, 1898.

also uses other avenues to communicate with health care professionals, including regular columns in prominent medical journals as well as a newsletter that it mails to physicians. In addition to publicizing belatedly discovered risk information, it may use these fora to influence best practices.

Some commentators suggest that physicians rarely bother to read the package insert closely or at all.[280] New information may require multiple avenues of dissemination coupled with the passage of time before it sinks into the collective medical consciousness and alters prescribing behavior. For example, the FDA communicated warnings to physicians and pharmacists in 1990 based on new information linking the antihistamine products Seldane® (terfenadine) and Hismanal® (astemizole) to potentially fatal drug interactions, but prescribing and dispensing patterns did not change for a few years until after the issuance of yet another warning and the publication of several research papers documenting this hazard.[281]

One recent study sponsored in part by the FDA found that labeling revisions and other efforts to communicate new risk information to health care professionals have essentially no impact on prescribing behavior.[282] Two years after the prescription heartburn remedy Propulsid® (cisapride) entered the market, the FDA revised the labeling in response to reports of serious cardiac side effects, but this had no apparent effect on its use.[283] Three years later, in the face of accumulating adverse event information, the FDA again revised the labeling to strengthen the black-box warning, and it ordered the manufacturer to send out 800,000 copies of a letter designed to draw attention to this new information.[284] The study attempted to quantify whether the second effort to disseminate clinically-relevant information altered prescribing behavior in the first year after

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280. *See* J.K. Littlejohn, *Package Insert: View of a Rural Town Practitioner*, 21 DRUG INFO. J. 63 (1987); Tanenbaum, *supra* note 45, at 37–38 ("It was treated as common knowledge [among physicians interviewed], for example, that the FDA's determinations of effectiveness were untrustworthy and that physicians did what they could to get around them."); Marlene Cimons, *FDA's Approval Process Faces Challenge in New Senate Bill*, L.A. TIMES, July 22, 1997, at A5 (describing a survey of oncologists that found "that 85% of the doctors said FDA labels have 'little influence' or 'practically no influence at all' in their treatment of patients").

281. *See* Raymond Woosley, *Opportunities in Phase IV to Improve Drug Development*, 52 FOOD & DRUG L.J. 185, 187 (1997). *But cf.* A.C. Rossi et al., *The Importance of Adverse Reaction Reporting by Physicians: Suprofen and the Flank Pain Syndrome*, 259 JAMA 1203, 1204 (1988) (applauding physicians for responding promptly to communications about newly discovered serious adverse reactions associated with another prescription drug).

282. *See* Walter Smalley et al., *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*, 284 JAMA 3036 (2000).

283. *See id.* at 3036 ("Despite the black-box warning [added in 1995], use of cisapride continued to increase in the United States....").

284. *See id.* at 3036–37. Moreover, this information had begun appearing in the medical literature two years before the FDA mandated the final labeling revision. *See id.* at 3039 & n.3.

publication, and it found "no material reduction" in the contraindicated uses of the drug.[285] The authors concluded that "[t]he exposure of [hundreds of thousands of] patients to inappropriate cisapride use, despite the prominent publication of case reports, label changes, and Dear Health Care Professional letters, highlights the need to develop more effective methods for modifying practice to reflect new information about a drug's risks and benefits."[286]

A commentary accompanying this study decried the loss of safe and effective drugs prompted by such prescribing errors,[287] and it blamed these sorts of mistakes on "the overwhelming amount of information on drugs."[288]

> In the last 25 years, the package inserts for new drugs have increased in length more than 5-fold. For example, the 2-page package insert for cisapride, when printed in 12-point font on 8.5 x 11 paper, is more than 10 pages long and contains more than 470 facts about the drug. Practicing physicians would have difficulty mastering all of this information for even one drug, much less the 40 to 100 medications that they regularly prescribe.[289]

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285. *See id.* at 3038–39. The manufacturer voluntarily withdrew the drug one year later. *See id.* at 3039.

286. *Id.* at 3039; *see also* C. Edward Evans et al., *Does a Mailed Continuing Education Package Improve Physician Performance? Results of a Randomized Trial in Antihypertensive Care*, 255 JAMA 501, 504 (1986); Stephen B. Soumerai et al., *Improving Drug Prescribing in Primary Care: A Critical Analysis of the Experimental Literature*, 67 MILBANK Q. 268, 293–94 (1989) (summarizing earlier research with similar results). Some commentators have urged the government to support efforts to counterbalance industry advertising. *See* Jerry Avorn & Stephen B. Soumerai, *Improving Drug-Therapy Decisions Through Educational Outreach: A Randomized Controlled Trial of Academically Based "Detailing,"* 308 NEW ENG. J. MED. 1457, 1462 (1983); Phil R. Manning et al., *Changing Prescribing Practices Through Individual Continuing Education*, 256 JAMA 230, 232 (1986); Stephen B. Soumerai & Jerry Avorn, *Principles of Educational Outreach ("Academic Detailing") to Improve Clinical Decision Making*, 263 JAMA 549, 555–56 (1990); *see also* Jonathan Lomas, *Retailing Research: Increasing the Role of Evidence in Clinical Services for Childbirth*, 71 MILBANK Q. 439, 459–61 (1993) (discussing similar strategies for implementing clinical practice guidelines).

287. *See* Raymond L. Woosley, *Drug Labeling Revisions—Guaranteed to Fail?*, 284 JAMA 3047, 3047 (2000) ("Many patients who have benefited from cisapride are now effectively deprived of that therapy....[T]his is not the first time that relatively safe drugs have been removed from the market because of the way that they were used in practice.").

288. *Id.*

289. *Id.* at 3048 (adding that, "since physicians must prescribe from multiple formularies that define which drugs patients can obtain under their medication insurance benefit, the number of drugs about which physicians must be thoroughly knowledgeable has become unacceptably large"). "It is wrong to expect that physicians can master through memorization the information necessary to practice good medicine." *Id.*; *see also* Lucian L. Leape et al., *Systems Analysis of Adverse Drug Events*, 274 JAMA 35, 40 (1995) ("The system with the highest number of errors was the system for disseminating drug knowledge, particularly to physicians. Errors attributed to lack of knowledge about drugs accounted for 91 (35%) of the 264 preventable ADEs and potential ADEs in this study.").

A couple of FDA officials openly chastised physicians for disregarding instructions in the labeling for newly approved drugs, and they warned that the agency might have to become more cautious in approving medical technologies because physicians seemed incapable of following directions.[290]

In a more measured response, the FDA announced that it has "engaged in several initiatives to make prescription drug labeling a better information source for health care practitioners-clearer, more informative, more accessible, and more consistent."[291] At the center of this effort is a proposal to significantly revise the format and content of the package insert. The agency's notice of proposed rulemaking, published in the waning days of the Clinton administration, begins by explaining that labeling "is the primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals."[292] The notice then asserts that the recent "increase in the amount, detail, and complexity of labeling information...has made it harder for health care practitioners to find specific information and to discern the most critical information in product labeling."[293] According to the FDA, several developments account for this increasing length and complexity, including technological advances in the products and the growing need for information about drug interactions and use in special populations.[294]

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290. *See* Peter Honig et al., Letter, *How Many Deaths Are Due to Medical Errors?*, 284 JAMA 2187, 2188 (2000).

> Errors involving pharmaceutical use are influencing our benefit-risk assessments. The recent market withdrawals of [five drugs] resulted, in part, from the health care system's inability to manage the known and preventable risks associated with these products. These experiences have catalyzed an evolution in our thinking on risk management and the evaluation of new drugs for approval. The FDA's risk assessment must evaluate both a drug's intrinsic safety profile as well as the ability of the health care system to adequately manage known toxicities. Unless effective risk management strategies and methods are brought to bear, additional effective drugs are likely to be withdrawn, and some drugs may never become available in the first place.

Id.; *see also* Lauran Neergaard, *FDA Tells Doctors to Heed Warnings on New Medicine*, HOUS. CHRON., Dec. 13, 2000, at 29; *Banned Medicines Riskier for Women*, HOUS. CHRON., Feb. 9, 2001, at 3 ("[I]ncreasingly frustrated FDA scientists say the main problem is that doctors ignored or never read warning labels that could have prevented deaths.").

291. 65 Fed. Reg. 38,563, 38,564 (June 21, 2000); *see also* Sarah Lueck, *FDA Frames Plan to Revamp Rules for Drug Labeling*, WALL ST. J., June 26, 2000, at B12.

292. 65 Fed. Reg. 81,082, 81,082 (Dec. 22, 2000); *see also id.* at 81,083 ("This information is intended to help ensure that health care practitioners are provided with a complete and accurate explanation...to facilitate their safe and effective prescribing. Thus, the [existing] regulations require prescription drug labeling to contain detailed information on various topics that may be important to practitioners.").

293. *Id.* at 81,083; *see also id.* ("[P]ractitioners expressed concern about the lack of ease in locating specific information among the extensive information presented.").

294. *See id.* In addition, the agency blames the threat of tort liability for cluttering the package insert with unnecessary warnings. *See id.* ("[T]he use of labeling in product

In an effort to help physicians cope with these changes, the FDA proposed some significant modifications to the package insert.[295] First, it plans to add a relatively short "highlights" section at the outset.[296] Second, the agency wants to include an "index" (more accurately a table of contents) before the comprehensive prescribing information.[297] Third, it plans to reorder the required sections in the package insert to move the most important and frequently referenced information closer to the beginning.[298] Fourth, the FDA wants to change the type face, such as requiring bold type in order to highlight subheadings and a minimum font size in order to improve readability.[299] The proposed rule calls for a format resembling the 1993 revisions to nutritional labels for food products[300] and the 1999 revisions to labels for nonprescription drug products.[301] Although physicians can better comprehend complex drug information than laypersons, they may share some of the same limitations when it comes to reading lengthy and dense text while operating under time constraints.

The FDA's proposal nowhere suggests that it may have placed excessive faith in the capacity of labeling to ensure rational prescribing. On the contrary, the agency still assumes that physicians regularly refer to package inserts,[302] particularly those accompanying new and unfamiliar products,[303] and that a more

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liability and medical malpractice lawsuits, together with increasing litigation costs, has caused manufacturers to become more cautious and include virtually all known adverse event information, regardless of its importance or its plausible relationship to the drug.").

295. *See id.* at 81,104 ("The objective of the proposed rule is to make it easier for health care practitioners to find, read, and use information important to the safe and effective prescribing of prescription pharmaceuticals (drugs and biologics) for patient treatment.").

296. *See id.* at 81,087–90 (describing proposed § 201.57(a)).

297. *See id.* at 81,090 (describing proposed § 201.57(b)).

298. *See id.* at 81,090–96.

299. *See id.* at 81,096 ("[T]he typically lengthy and undifferentiated format of prescription drug labeling makes it difficult to locate and read specific information."); *id.* (explaining that an 8-point "minimum type size would make it easier for practitioners to read labeling information and thus help to ensure the safe and effective use of prescription drug products," but conceding that a still larger size would be preferable).

300. *See* 58 Fed. Reg. 2066–926 (Jan. 6, 1993) (codified as amended in scattered sections of 21 C.F.R. pt. 101 (2001)).

301. *See* 64 Fed. Reg. 13,254, 13,286 (Mar. 17, 1999) (codified at 21 C.F.R. § 201.66 (2001)).

302. *See* 65 Fed. Reg. 81,082, 81,104 (Dec. 22, 2000) ("[A] 1994 FDA survey of physicians found that 42 percent referred to labeling at least once a day, 33 percent less often than once a day but more often than once a week, and 25 percent once a week or less."). The agency conceded, however, that physicians may "spend, on average, only 30 seconds referring to labeling (once the labeling is at hand)." *Id.*

303. *See id.* ("In FDA's survey of physicians, newness of the product was the factor most often rated by physicians as 'very likely' to trigger referral to prescription drug labeling."). The agency reiterated this point to justify its decision to apply the proposed new formatting requirements only to newer drugs. *See id.* at 81,098 (noting that "physicians are more likely to refer to the labeling of recently approved products," whose labeling "is likely to be longer and more complex than that of older products").

user-friendly format will reduce the time currently wasted in searching for particular information,[304] facilitate the selection of the most effective therapies and dosages, and reduce the occurrence of preventable side effects as well as other prescribing errors.[305] Several critics warned that adding the proposed "highlights" section might lead some physicians to rely on this abridged information,[306] but they assume that prescribers would otherwise attentively read the long version. As the FDA correctly noted in responding to this concern, "[i]t is unrealistic to expect practitioners to read every word of product labeling each time they reference it, regardless of how desirable it may be for them to do so."[307] Nonetheless, the agency's optimistic assumption that most physicians rely to some extent on the package insert seems naive. If one started from the opposite premise, then the risk-benefit judgments made by the agency when it decides whether to approve new medical technologies might turn out differently.

Although disputes about warnings typically pit manufacturers against the agency, on rare occasions medical professionals may challenge an FDA labeling decision. In the early 1970s, after the agency proposed requiring a warning of cardiac risks associated with oral hypoglycemic drugs, a group of almost two hundred physicians challenged the decision because of questions about the methodology of the large-scale RCT that prompted it.[308] After noting the unusual posture of this litigation (namely, a petition filed by physicians rather than manufacturers and assailing the FDA's proposal for violating statutory provisions that prohibit misleading labeling by manufacturers), a federal court rejected the petition for review as premature.[309] Nonetheless, the effort demonstrates the significance that health care professionals may attach to statements appearing in the package insert and concerns that the agency had distorted this source of information about oral hypoglycemic drugs by premising its decision on allegedly flawed research.

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304. *See id.* at 81,104 (calculating cumulative time savings "[i]f the new format reduced by 15 seconds the amount of time physicians needed to find information on prescription drug labeling").

305. *See id.* at 81,105.

306. *See id.* at 81,087 ("Several comments contended that practitioners might rely solely on this section and fail to read the comprehensive prescribing information.").

307. *Id.* ("Therefore, the FDA is proposing to add the highlights section to prescription drug labeling to draw attention to those sections of the labeling that are most important, and to do so in a way that readily facilitates and encourages more detailed followup.").

308. *See* Gina Bari Kolata, *Controversy over Study of Diabetes Drugs Continues for Nearly a Decade*, 203 SCIENCE 986 (1979).

309. *See* Bradley v. Weinberger, 483 F.2d 410, 415 (1st Cir. 1973); *see also* Forsham v. Harris, 445 U.S. 169, 177–86 (1980) (rejecting a Freedom of Information Act request by the same group of physicians seeking access to the underlying data). After some further skirmishing, the FDA issued a warning requirement based on the disputed study. *See* 49 Fed. Reg. 14,303, 14,331 (Apr. 11, 1984) (codified at 21 C.F.R. § 310.517 (2001)).

2. Restrictions on Advertising

The FDA strictly limits advertising for prescription drugs and medical devices. Once a new therapeutic product receives marketing clearance from the agency, it can be promoted only for the indications set forth in the approved labeling. Physicians, however, remain free to use these drugs and medical devices for other purposes.[310] In the early 1990s, the FDA became concerned that some manufacturers were indirectly promoting off-label uses, for instance by providing health care professionals with "enduring materials" (namely, textbooks and reprints of published articles) and by sponsoring CME programs and scientific symposia featuring discussions about such uses of their products. In addition to bringing enforcement actions against particular companies, the agency issued a "draft policy statement" in 1992 to inform the industry that it might regard such activities as unlawful product promotions unless certain steps were taken to ensure editorial independence.[311] The FDA's draft policy statement evolved into a pair of guidance documents on enduring materials published in 1996.[312]

The agency's initiatives against off-label promotion through the distribution of enduring materials and CME programs triggered important legislative and judicial responses. First, a public interest organization representing a group of physicians lodged a constitutional challenge against the FDA's restrictions.[313] As noted earlier, a federal district court held that the policies ran afoul of the First Amendment, in large part because it concluded that the government lacked any substantial interest in preventing the dissemination of

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310. *See* Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350–51 & n.5 (2001); Lars Noah, *Constraints on the Off-Label Uses of Prescription Drug Products*, 16 J. PRODS. & TOXICS LIAB. 139, 140–46 (1994).

311. *See* 57 Fed. Reg. 56,412 (Nov. 27, 1992); *see also* David G. Adams, *FDA Regulation of Communications on Pharmaceutical Products*, 24 SETON HALL L. REV. 1399, 1409–17 (1994) (describing the origins of this policy, and defending its constitutionality); Lars Noah & Barbara A. Noah, *Liberating Commercial Speech: Product Labeling Controls and the First Amendment*, 47 FLA. L. REV. 63, 107–11 (1995) (arguing that the CME policy violated the constitution); Charles J. Walsh & Alissa Pyrich, *FDA Efforts to Control the Flow of Information at Pharmaceutical Industry-Sponsored Medical Education Programs: A Regulatory Overdose*, 24 SETON HALL L. REV. 1325, 1352–63 (1994) (criticizing the FDA's restrictions as excessive).

312. *See* 61 Fed. Reg. 52,800 (Oct. 8, 1996). The FDA published a separate guidance document on CME programs one year later. *See* 62 Fed. Reg. 64,074 (Dec. 3, 1997).

313. *See* Washington Legal Found. v. Kessler, 880 F. Supp. 26, 31–32 (D.D.C. 1995) (finding that a public interest group had standing to litigate on behalf of its member physicians because, even though they did not have the same financial stake as drug and device manufacturers, they had an interest in receiving information about off-label uses); *see also id.* at 36 ("The fact that this suit is being brought by *doctors* who have been prevented from receiving information rather than the *manufacturers* with whose conduct the FDA policy primarily interferes lends further credence to plaintiff's contention" that the draft policy statement is sufficiently final for judicial review.).

misleading information to physicians.[314] The court noted that "[a] physician's livelihood depends upon the ability to make accurate, life-and-death decisions based upon the scientific evidence," and it therefore concluded that physicians were "certainly capable of critically evaluating journal articles or textbook reprints that are mailed to them, or the findings presented at CME seminars."[315] The judge did not bother to cite any research to support this seemingly self-evident proposition.[316]

At the same time, Congress enacted significant amendments to the agency's enabling statute, including a provision that authorized the distribution of enduring materials under certain limited circumstances.[317] After further briefing,

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314. *See* Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 74 (D.D.C. 1998), *order amended*, 36 F. Supp. 2d 16, 19 (D.D.C. 1999), *order amended sub nom.* Washington Legal Found. v. Henney, 56 F. Supp. 2d 81, 87 (D.D.C. 1999), *vacated in part and appeal dismissed*, 202 F.3d 331 (D.C. Cir. 2000). The court, however, rejected the plaintiffs' claim that the distribution of enduring materials or sponsorship of CME deserved even more constitutional protection as scientific rather than merely commercial speech. *See Friedman*, 13 F. Supp. 2d at 62–64. As one scholar explained, such regulations violate the "principle of epistemological humility" at the core of the First Amendment. *See* Martin H. Redish, *Product Health Claims and the First Amendment: Scientific Expression and the Twilight Zone of Commercial Speech*, 43 VAND. L. REV. 1433, 1455, 1435 (1990) ("[A]ny attempt by the government to impose a national scientific orthodoxy could undermine or inhibit the advance of scientific knowledge, thus undermining a key value of the first amendment."); *id.* at 1443 ("[V]iewed from the broad perspective of history, any attempt by the government to lock in a prevailing scientific consensus is likely to be either futile or dangerous.").

315. *Friedman*, 13 F. Supp. 2d at 70; *see also id.* ("[I]n light of the fact that the FDA does not question a physician's evaluative skills when the information comes from a source other than a drug manufacturer, concerns about a physician's ability to critically evaluate materials presented to him is not a 'substantial interest.'"); Edmund Polubinski III, Note, *Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of "Off-Label" Use*, 83 VA. L. REV. 991, 1009 n.106 (1997) (noting the "undeniable dissonance between the agency's justification and its position that physicians may determine which treatments to prescribe and that some off-label uses represent the standard of care"); *id.* at 1025 ("[I]n some respects the information might be less misleading when distributed by a manufacturer. For example, if a recipient physician knows the source of a manufacturer distribution, he or she is likely to be fully aware of the sender's interest in the material and therefore read with a more skeptical eye."). This apparent inconsistency in the agency's position is, however, easily explained: even if it would have preferred to restrict physicians' access to any published information about off-label uses, the FDA only has the authority to regulate information that accompanies products falling within its jurisdiction.

316. *See* Glenn C. Smith, *Avoiding Awkward Alchemy in the Off-Label Drug Context and Beyond: Fully-Protected Independent Research Should Not Transmogrify into Mere Commercial Speech Just Because Product Manufacturers Distribute It*, 34 WAKE FOREST L. REV. 983, 1039 n.334 (1999) (suggesting that this "view of physician competence would need some documentation or authority (which the court did not provide)").

317. *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 401(a), 111 Stat. 2296, 2356–64 (codified at 21 U.S.C. § 360aaa (2000))

the federal district court concluded that this provision also violated the Constitution's guarantees of free speech.[318] On appeal, the FDA took the position that its policies, as revised in light of the statutory amendment, simply provided a safe harbor for certain kinds of communications and did not of their own force prohibit other types of communications, which led the court to dismiss the appeal as moot.[319] Nonetheless, the controversy over the dissemination of enduring materials reveals that judges and legislators may place unjustified faith in the capacity of physicians to evaluate critically material that comes from the industry.

In unusual cases, persons other than the product seller may communicate prescribing information that deviates from the FDA-approved labeling. Just before the controversial abortion drug Mifeprex® (mifepristone) reached the United States market, pro-choice groups sent letters to physicians recommending a less cumbersome treatment regimen in an effort to expand use,[320] while pro-life groups sent letters to physicians providing more dramatic risk information in an effort to discourage use.[321] In addition, a few weeks before approval, the manufacturer of the ulcer drug Cytotec® (misoprostol), which doctors widely prescribe off-label to induce labor and is specifically identified in the labeling for Mifeprex as needed to complete the abortion, sent a letter to health care professionals warning that its drug should never be administered to pregnant women, a position that the company clarified a few months later under pressure from the FDA.[322] It seems

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[hereinafter FDAMA]. The FDA issued implementing regulations one year later, which superseded its guidelines on enduring materials. *See* 63 Fed. Reg. 64,556 (Nov. 20, 1998) (codified at 21 C.F.R. pt. 99 (2001)).

318. *See Henney*, 56 F. Supp. 2d at 87; *see also id.* at 86 (conceding that many of FDAMA's provisions "directly advance the FDA's stated goal of ensuring that physicians receive accurate and balanced information," but reiterating that this "is not a substantial interest" in the first place). It is difficult to defend the district court's conclusion that the government lacked a substantial interest in protecting health care providers from misleading information. Instead, because physicians are a sophisticated audience, measures short of broadly prohibiting such communications rendered the FDA's original policies vulnerable under the final prong of the commercial speech test, but then FDAMA's more carefully drawn limitations probably should have survived on that score.

319. *See* Washington Legal Found. v. Henney, 202 F.3d 331, 335–36 (D.C. Cir. 2000); *see also* Washington Legal Found. v. Henney, 128 F. Supp. 2d 11, 15 (D.D.C. 2000) (clarifying that nothing remained of the injunction); Lars Noah, *What's Wrong with 'Constitutionalizing Food and Drug Law,'* 75 TUL. L. REV. 137, 146–48 (2000) (recounting the course of this litigation, and questioning the "safe harbor" interpretation accepted by the court on appeal).

320. *See* Sarah Lueck, *Groups Offer Abortion-Drug Variations*, WALL ST. J., Oct. 30, 2000, at B2; *see also* Eric A. Schaff et al., *Low-Dose Mifepristone Followed by Vaginal Misoprostol at 48 Hours for Abortion up to 63 Days*, 61 CONTRACEPTION 41, 45 (2000).

321. *See* Rachel Zimmerman, *Wrangling over Abortion Intensifies as RU486 Pill Nears the Market*, WALL ST. J., Nov. 14, 2000, at B1 (reporting that one group "sent 150,000 letters to obstetrician/gynecologists and family-practice physicians warning of possible adverse effects").

322. *See* Marie McCullough, *Firm Clarifies Its Warning on Drug Also Used to Induce Labor*, PHIL. INQUIRER, Jan. 4, 2001, at A3; *see also* Michael A. Friedman, Letter, *Manufacturer's Warning Regarding Unapproved Uses of Misoprostol*, 344 NEW ENG. J.

unlikely that any other drug product will generate such competing efforts to influence prescribing behavior,[323] especially so soon after FDA approval, but this episode demonstrates that physicians may receive conflicting off-label drug information from a variety of sources.

Finally, favorable comparative research may provide the impetus for promotional efforts. Pharmaceutical manufacturers increasingly sponsor randomized controlled trials pitting their product against a competitor's drug (or another form of treatment) in the hope of demonstrating superiority in relative safety, effectiveness, and/or cost.[324] Until recently, the FDA strictly limited the use of such claims.[325] In 1997, Congress liberalized these restrictions by allowing drug companies to disseminate "health care economic information" so long as it is based on "competent and reliable scientific evidence."[326] Manufacturers could not, however, provide pharmacoeconomic information to individual health care professionals because of congressional concerns that physicians would not have the time or skill needed to interpret research on the cost effectiveness of drugs.[327] This more paternalistic stance stands in sharp contrast to the provision in the same

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MED. 61 (2001) ("We particularly wish to clarify the timing of the letter dated August 23. The fact that it was distributed just over a month before the FDA approval of mifepristone was entirely coincidental."); *cf.* Ralph W. Hale & Stanley Zinberg, Editorial, *Use of Misoprostol in Pregnancy*, 344 NEW ENG. J. MED. 59, 60 (2001) ("The timing of the letter, just weeks before the FDA announced its approval of mifepristone, left many people wondering whether there were other motivations for Searle's actions.").

323. *See* Lars Noah, *A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics*, 36 WAKE FOREST L. REV. 571 (2001).

324. *See* Thomas M. Burton, *Older Treatment for Manic Illness May Be Superior*, WALL ST. J., Dec. 12, 2000, at B1 (reporting on research sponsored by the manufacturer of Zyprexa which found that another drug works just as well in treating biploar disorder with fewer side effects and at half the cost); *see also* Pfizer, Inc. v. Miles, Inc., 868 F. Supp. 437, 452–57 (D. Conn. 1994) (reviewing a Lanham Act claim for misleading comparative drug advertising); *supra* notes 181–83 and accompanying text (discussing pharmacoeconomic research).

325. *See* 21 C.F.R. § 202.1(e)(6)(ii) (2001); David A. Kessler et al., *Therapeutic-Class Wars—Drug Promotion in a Competitive Marketplace*, 331 NEW ENG. J. MED. 1350, 1352 (1994); Peter J. Neumann et al., *The FDA and Regulation of Cost-Effectiveness Claims*, HEALTH AFF., Fall 1996, at 54, 59–61 (criticizing the agency's traditional demand for RCTs to substantiate pharmacoeconomic claims); *cf.* David Henry & Suzanne Hill, Editorial, *Comparing Treatments: Comparison Should Be Against Active Treatments Rather Than Placebos*, 310 BRIT. MED. J. 1279 (1995) (arguing that governments should sponsor comparative efficacy studies).

326. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 114(a), 111 Stat. 2296, 2312 (codified at 21 U.S.C. § 352(a)). The statute defined "health care economic information" as "any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention." *Id.*; *see also* Note, *Will Health Care Economic Information Lead to Therapeutic-Class Warfare or Welfare?*, 111 HARV. L. REV. 2384, 2401 (1998) (calling for greater FDA guidance in this area).

327. *See* H.R. REP. NO. 105-310, at 65 (1997).

statute that had liberalized the rules on the distribution of enduring materials that discuss off-label uses.

3. Intellectual Property Rules

In many contexts, information represents a "public good," which means that it will be undersupplied unless the government mandates its production or rewards those who produce it.[328] The FDA's premarket review mechanisms and other controls generate substantial information about drugs and medical devices. No similar regulatory regime exists with regard to surgical techniques and other types of therapeutic interventions,[329] which has led a few commentators to suggest extending federal regulatory authority into this area.[330]

Intellectual property protections offer a different mechanism for generating information about medical advances. The patent laws attempt to encourage innovation and the dissemination of new technology by rewarding those who first publicize their inventions.[331] Again, the availability of patent protection for pharmaceutical products and medical devices has facilitated substantial private investments in the production of information related to those therapeutic interventions.[332] In some cases, Congress has supplemented these

328. *See* Daniel A. Farber, *Free Speech Without Romance: Public Choice and the First Amendment*, 105 HARV. L. REV. 554, 558–61 (1991); *see also* Havighurst, *supra* note 213, at 348; Mark V. Pauly, *The Public Policy Implications of Using Outcome Statistics*, 58 BROOK. L. REV. 35, 46 (1992); Sage, *supra* note 16, at 1777 n.282 ("Much health care information, including informal 'best practices' as well as the results of empirical investigations, falls into this [public good] category.").

329. *See* Mehlman, *supra* note 271, at 820–21; Thomas Necheles, *Standards of Medical Care: How Does an Innovative Medical Procedure Become Accepted?*, 10 LAW MED. & HEALTH CARE 15, 17 (1982) ("The FDA has long been accepted as the arbiter of the safety and effectiveness of drugs. No such arbiter exists in the field of innovative medical procedures."); David H. Spodick, *Numerators Without Denominators: There Is No FDA for the Surgeon*, 232 JAMA 35, 35–36 (1975); *see also* Council on Ethical & Judicial Aff., AMA, *Ethical Issues in the Patenting of Medical Procedures*, Rep. No. 1-A-95, at 63 (1995) (arguing that peer review appropriately serves as the "primary regulatory mechanism for medical processes").

330. *See* Note, *The Open-Ended Investigation: A Method for Regulation of New Medical Services*, 91 YALE L.J. 550, 566–67 (1982); *cf.* J.P. Bunker et al., *Surgical Innovation and Its Evaluation*, 200 SCIENCE 937, 941 (1978) (calling on the biomedical research community to generate the missing information); John E. Wennberg, *The Paradox of Appropriate Care*, 258 JAMA 2568, 2569 (1987) (same).

331. *See* Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 484 (1974); Fujikawa v. Wattanasin, 93 F.3d 1559, 1563-64, 1567-69 (Fed. Cir. 1996); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed. Cir. 1991) (explaining that one purpose of the "written description" requirement was to disseminate an invention to the public); *see also* Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1028–29 (1989).

332. *See* William D. Noonan, *Patenting Medical Technology*, 11 J. LEGAL MED. 263, 271–72 (1990); Sage, *supra* note 16, at 1774; *see also* Phanesh Koneru, *To Promote the Progress of Useful Art[icle]s?: An Analysis of the Current Utility Standards of*

incentives by granting product manufacturers additional market exclusivity periods in order to generate valuable but otherwise undersupplied biomedical information, such as prescribing information for pediatric uses of approved drugs.[333] Congress used the same strategy, along with special tax breaks, to encourage industry research into "orphan drug" indications where the small expected user population otherwise would deter investments in R&D.[334]

In the last decade, controversy has erupted over efforts to patent advances in surgical techniques.[335] In 1996, Congress responded by amending the statute to exempt health care providers from any liability for infringing patented medical procedures,[336] which effectively rendered novel medical techniques unpatentable subject matter. Several commentators have objected that this legislation may reduce the incentive to undertake research and disseminate information about the safety and effectiveness of innovative procedures.[337]

Pharmaceutical Products and Biotechnological Research Tools, 38 IDEA 625, 666 (1998) (explaining that the patent laws "appear to provide sufficient incentive to *other* inventors who find new uses to already disclosed products").

333. *See* 21 U.S.C. § 355a (2000); Nat'l Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 41 (D.D.C. 1999) (concluding that it would disserve the public interest to grant a preliminary injunction, based on alleged procedural errors, against the FDA's efforts to implement this "incentive for the conduct of important pharmaceutical testing–which is not otherwise required of drug manufacturers"); Kurt R. Karst, Comment, *Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry*, 49 AM. U. L. REV. 739 (2000); Rachel Zimmerman, *Pharmaceutical Firms Win Big on Plan to Test Adult Drugs on Kids*, WALL ST. J., Feb. 5, 2001, at A1 ("That law, by giving drug makers an incentive to test on children, is producing important new prescribing information for pediatricians...."). Congress recently extended this program for another five years. *See* Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002).

334. *See* 21 U.S.C. §§ 360aa–360ee (2000); 21 C.F.R. pt. 316 (2001); Baker Norton Pharm., Inc. v. FDA, 132 F. Supp. 2d 30, 31 (D.D.C. 2001) (noting that these incentives appear to have worked); *see also* Robert A. Bohrer & John T. Prince, *A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act*, 12 HARV. J.L. & TECH. 365, 367–72 (1999); David D. Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125, 126–33 (2000).

335. *See* Council on Ethical & Judicial Aff., AMA, *Ethical Issues in the Patenting of Medical Procedures*, 53 FOOD & DRUG L.J. 341 (1998); Gregory F. Burch, Note, *Ethical Considerations in the Patenting of Medical Processes*, 65 TEX. L. REV. 1139, 1152–61 (1987); Edward Felsenthal, *Medical Patents Trigger Debate Among Doctors*, WALL ST. J., Aug. 11, 1994, at B1.

336. *See* 35 U.S.C. § 287(c) (2000); Weldon E. Havins, *Immunizing the Medical Practitioner 'Process" Infringer: Greasing the Squeaky Wheel, Good Public Policy, or What?*, 77 U. DET. MERCY L. REV. 51 (1999).

337. *See* Cynthia M. Ho, *Patents, Patients, and Public Policy: An Incomplete Intersection at 35 U.S.C. § 287(c)*, 33 U.C. DAVIS L. REV. 601, 613–18, 648–50 (2000); Chris J. Katopis, *Patients v. Patents?: Policy Implications of Recent Patent Legislation*, 71 ST. JOHN'S L. REV. 329, 358, 397–99 (1997); Joel J. Garris, Note, *The Case for Patenting Medical Procedures*, 22 AM. J.L. & MED. 85, 92–93, 95–97 (1996).

Absent comparable incentives for generating information about the whole range of available therapies, health care professionals may receive a distorted picture of the relative safety and effectiveness of their different options.[338] This asymmetrical knowledge base–where a great deal is known about both the risks and the benefits of drugs but fairly little about nonpharmaceutical treatments–may result in suboptimal therapeutic choices.[339] For instance, a recent clinical trial demonstrated that brain surgery effectively treated patients who suffered from temporal-lobe epilepsy and did not respond to anticonvulsants.[340] Although the technique has long existed, few eligible patients underwent this surgical procedure, in part because previously no one had undertaken an RCT to establish its efficacy.[341] Of course, the new study may not rapidly alter existing treatment patterns, but knowledge production must precede diffusion into practice.

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338. *See* H. David Banta & Stephen B. Thacker, *The Case for Reassessment of Health Care Technology: Once Is Not Enough*, 264 JAMA 235, 236–37, 239 (1990) (explaining that most RCTs focus on new drugs, resulting in less information about older technologies and surgical techniques); Sage, *supra* note 16, at 1775 ("[S]ellers of proprietary products have strong incentives to market their merchandise, further skewing available practice information toward one subset of therapies."); *see also* Steven H. Woolf, *The Need for Perspective in Evidence-Based Medicine*, 282 JAMA 2358, 2359 (1999) ("The literature includes countless head-to-head trials of drugs or procedures, but it provides no 'big picture' comparison of the net health effect of competing medical and public health strategies."); *Academy Issues Guidelines for Treatment of ADHD*, WASH. POST, Oct. 1, 2001, at A14 ("Evidence favoring the use of medication—specifically stimulants such as...Ritalin, or amphetamines–is stronger than evidence on behavior therapy, the guidelines say.").

339. *Cf.* Peter Huber, *The Old-New Division in Risk Regulation*, 69 VA. L. REV. 1025, 1073 (1983) ("Every regulation of one source of risk will cause some secondary 'risk displacement,' encouraging producers or consumers to favor alternative, less stringently regulated processes or products that will themselves be risky in some degree."); Schuck, *supra* note 21, at 948 ("The principal goals of informed consent doctrine–to promote and protect patient autonomy and to improve the quality of both patients' and physicians' treatment decisions–cannot be achieved unless the information about the risks associated with various treatment (and nontreatment) alternatives is reliable...."); Trinder, *supra* note 157, at 219 ("[T]he uneven distribution of the evidence base...has implications for what services may be purchased or provided.").

340. *See* Samuel Wiebe et al., *A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy*, 345 NEW ENG. J. MED. 311 (2001).

341. *See id.* at 312 ("Paradoxically, surgery appears to be grossly underused....Many clinicians...view surgery as a last resort for patients with intractable epilepsy."); *id.* ("The absence of robust evidence supporting the safety and efficacy of surgery for epilepsy figures prominently among the possible reasons for this view....[D]evelopers of practice guidelines for surgery for epilepsy have been unable to make strong recommendations for clinical practice."); *see also* Jerome Engel, Editorial, *Finally, A Randomized, Controlled Trial of Epilepsy Surgery*, 345 NEW ENG. J. MED. 365, 365 (2001) ("[A]n important obstacle to surgery's taking what many believe to be its rightful place in the therapeutic armamentarium for epilepsy has been our failure to apply the gold standard for the evaluation of therapeutic efficacy—the [RCT]."); Nicholas J. Petrelli, Editorial, *Clinical Trials Are Mandatory for Improving Surgical Cancer Care*, 287 JAMA 377 (2002).

B. Tort Litigation

The courts also play a role in encouraging the generation, dissemination, and assimilation of biomedical information. As mentioned previously in connection with the standards used to evaluate the admissibility of expert testimony,[342] the courts also sometimes make unrealistic assumptions about how physicians become knowledgeable. Greater attention to the insights of EBM may facilitate the resolution of tort litigation involving medical technologies and medical practice. In turn, the courts may help to encourage the production of biomedical research and perhaps also persuade physicians to align their practice patterns more closely with the ideals of evidence-based medicine.

1. Products Liability

Apart from FDA requirements, strict products liability law affects how manufacturers label and design products utilized in health care delivery. (In contrast, as discussed in the next section, tort law uses the less exacting standards of medical malpractice to resolve personal injury claims arising from surgical and other medical procedures.[343]) The courts demand that sellers of prescription drugs and medical devices communicate warnings to health care professionals. Indeed, because physicians and other "learned intermediaries" must make the judgment about which therapeutic agents to select for a particular patient, sellers of these medical technologies generally have no obligation to warn the patients directly.[344] Along similar lines, a prescription drug or medical device may be defectively designed if no reasonable health care provider, fully informed of the risks and benefits of the chosen design, would select the product for any class of patients.[345] Some commentators have criticized these tests for warning and design defect claims because doctors are "unable to keep up with the daily changes in the state of medical knowledge."[346]

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342. *See supra* notes 27–32 and accompanying text.

343. *See infra* Part IV.B.2; *see also* Hoven v. Kelble, 256 N.W.2d 379, 391–93 (Wis. 1977) (declining to impose strict liability for medical services); Frank J. Vandall, *Applying Strict Liability to Professionals: Economic and Legal Analysis*, 59 IND. L.J. 25, 54–55 (1983).

344. *See* Toole v. Baxter Healthcare Corp., 235 F.3d 1307, 1313–14 (11th Cir. 2000); Talley v. Danek Med., Inc., 179 F.3d 154 (4th Cir. 1999); Thomas v. Hoffman-LaRoche, Inc., 949 F.2d 806, 811 (5th Cir. 1992); Vitanza v. Upjohn Co., 778 A.2d 829 (Conn. 2001); Martin v. Hacker, 628 N.E.2d 1308, 1311 (N.Y. 1993).

345. *See* RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6(c) & cmt. f (1998); *see also* Violette v. Smith & Nephew Dyonics, Inc., 62 F.3d 8, 13 (1st Cir. 1995) (holding that a jury could find an endoscopic device used to treat carpal tunnel syndrome defectively designed because a clearly safer surgical procedure existed).

346. Susan A. Casey, Comment, *Laying an Old Doctrine to Rest: Challenging the Wisdom of the Learned Intermediary Doctrine*, 19 WM. MITCHELL L. REV. 931, 957 (1993); *see also* Freeman v. Hoffman-LaRoche, Inc., 618 N.W.2d 827, 839–40 (Neb. 2000) ("[T]he reasonable physician test...requires fact finders to presume that physicians have as much or more of an awareness about a prescription drug product as the manufacturer."); *id.* ("The

Courts sometimes struggle to determine precisely when a seller should have known that its product presented a risk of injury, whether the failure to provide a warning caused the plaintiff's injury given the fact that physicians may learn of new risk information from a variety of other sources, and whether the content and method selected for communicating the information was adequate in light of limitations in the way health care professionals discover and assimilate new information. Courts do not impose a duty to warn of unknowable risks associated with drugs or medical devices.[347] It is difficult, of course, to identify at what point knowledge about a putative hazard gives rise to a duty to warn. Some courts have found such a duty on the basis of extremely weak evidence that a substance may have caused an injury.[348] For instance, in one case a court held that a reasonable jury could have found a failure to warn of a risk not revealed during clinical trials because of knowledge that a chemically similar product created such a risk.[349] Other courts have demanded greater substantiation of a risk allegedly posed by a product before imposing a duty to warn of that risk.[350]

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test also ignores concerns of commentators that physicians tend to prescribe drugs they are familiar with or for which they have received advertising material...."); Teresa Moran Schwartz, *Prescription Products and the Proposed Restatement (Third)*, 61 TENN. L. REV. 1357, 1382–83 (1994); Jeffrey D. Winchester, Note, *Section 8(c) of the Proposed Restatement (Third) of Torts: Is It Really What the Doctor Ordered?*, 82 CORNELL L. REV. 644, 675 (1997) ("It is practically impossible for a doctor to keep abreast of the broad field of medical product innovation. Doctors are busy people, with very demanding caseloads, and it is often difficult for them to keep up with new developments, even in their own fields, much less in the field of pharmacology." (footnotes omitted)).

347. *See* Moore v. Vanderloo, 386 N.W.2d 108, 116 (Iowa 1986); Castrignano v. E.R. Squibb & Sons, Inc., 546 A.2d 775, 782 (R.I. 1988) (refusing to hold manufacturer of DES liable "for failure to warn of risks inherent in a drug [because] it neither knew nor could have known by the application of scientific knowledge available at the time of distribution that the drug could produce the undesirable effects suffered by plaintiff"); *see also* RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6 cmt. g (1998); Kathleen H. Wilson, Note, *The Liability of Pharmaceutical Manufacturers for Unforeseen Adverse Drug Reactions*, 48 FORDHAM L. REV. 735, 745–50 (1980).

348. *See, e.g.*, Hermes v. Pfizer, Inc., 848 F.2d 66, 68 (5th Cir. 1988) (adverse event reports); Wells v. Ortho Pharm. Corp., 788 F.2d 741, 745–46 (11th Cir. 1986) (manufacturer of spermicide had duty to warn of possible teratogenicity notwithstanding the FDA's conclusion that these drugs did not cause birth defects); Vassallo v. Baxter Healthcare Corp., 696 N.E.2d 909, 920–21 (Mass. 1998) (complaint files).

349. *See* Wagner v. Roche Labs., 671 N.E.2d 252, 256–58 (Ohio 1996) (Accutane); *see also* Mulligan v. Lederle Labs., 786 F.2d 859, 864–65 (8th Cir. 1986) (sustaining a verdict for the plaintiff where the manufacturer previously had received reports of similar but not identical adverse reactions); Barson v. E.R. Squibb & Sons, 682 P.2d 832, 836 (Utah 1984) (reports that progesterone caused birth defects should have alerted manufacturer of progesterone-derivative of teratogenic potential).

350. *See, e.g.*, Doe v. Miles Labs., Inc., 927 F.2d 187, 194 (4th Cir. 1991) (holding that there was no duty to warn where "only one case of AIDS was reported that could possibly have been related to Factor IX treatment...[and] only a few AIDS cases were related to the use of any blood factor concentrate"); Novak v. United States, 865 F.2d 718, 726 (6th Cir. 1989) (concluding that warnings accompanying swine flu vaccine were not

In one recent products liability case, the California Supreme Court attempted to define this knowability threshold. The majority explained that a pharmaceutical company would have a duty to warn only of "reasonably scientifically knowable risks."[351] Although it equivocated in further defining this test, the court suggested that the inquiry would focus on how a reasonable "scientist conducting state-of-the-art research" would interpret a body of data.[352] The standard apparently does not, however, ask how such a scientist would interpret the data against the totality of other research casting light on the particular question.[353]

The majority conceded that, "if state-of-the-art scientific data concerning the alleged risk was fully disclosed to the FDA and it determined, after review, that the pharmaceutical manufacturer was not permitted to warn," then "the FDA's conclusion that there was, in effect, no 'known risk' is controlling."[354] Even though the decision to defer to the agency's determination makes perfect sense,[355] it seems odd to anoint the FDA as the arbiter of what is "known," especially insofar as its regulatory decisions sometimes reflect an effort to pursue collateral goals.[356] A partial dissent in the case emphasized that the majority's standard "fails to recognize, much less deal with, the complexity of scientific evaluations,"[357] and it

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inadequate for failing to alert persons of risk of autoimmune disease because there was "insufficient medical evidence" of causation); Smith v. Ortho Pharm. Corp., 770 F. Supp. 1561, 1582 (N.D. Ga. 1991) (rejecting failure-to-warn claim because there was no "reasonably reliable" evidence that spermicide caused birth defects); Finn v. G.D. Searle & Co., 677 P.2d 1147, 1153 (Cal. 1984) ("Knowledge of a potential side effect which is based on a single isolated report of a possible link between a prescription drug and an injury may not require a warning.").

351. Carlin v. Superior Court, 920 P.2d 1347, 1349 (Cal. 1996) ("[W]e have expressly and repeatedly applied a strict liability standard to manufacturers of prescription drugs for failure to warn of known or reasonably scientifically knowable risks.").

352. *Id.* at 1353 ("[W]hen a plaintiff's claim is based on an allegation that a particular risk was 'reasonably scientifically knowable,' an inquiry may arise as to what a reasonable scientist operating in good faith should have known under the circumstances of the evidence.").

353. *See id.* at 1351 ("[A] reasonably prudent manufacturer might reasonably decide that the risk of harm was such as not to require a warning as, for example, if the manufacturer's own testing showed a result contrary to that of others in the scientific community. Such a manufacturer might escape liability under negligence principles.").

354. *Id.* at 1353.

355. *See id.* at 1365 n.4 (Kennard, J., concurring in part and dissenting in part); Lars Noah, *Rewarding Regulatory Compliance: The Pursuit of Symmetry in Products Liability*, 88 GEO. L.J. 2147, 2153–58, 2165 (2000).

356. For instance, during negotiations over the labeling of transdermal nicotine patches, manufacturers sought to include a stringent pregnancy warning concerning the teratogenicity of nicotine, but the FDA opted for a milder warning evidently because it did not want to discourage women who would otherwise have smoked during their pregnancy from attempting a cessation program using a patch. *See Nicotine Replacement Product*, F-D-C REP. ("The Pink Sheet"), July 20, 1992, at 8, 9.

357. *Carlin*, 920 P.2d at 1360 (Kennard, J., concurring in part and dissenting in part) ("[T]he quality of scientific evidence 'may range from extremely vague to highly

recommended instead a duty to warn "only of those risks supported by credible scientific evidence or that upon reasonable inquiry would be supported by credible scientific evidence."[358]

If a plaintiff's prescribing or treating physician testifies that he or she already knew of the information that the seller had failed to convey adequately, and proceeded in the face of that known risk, then any inadequacy in the warning could not have caused the plaintiff's injury.[359] Physicians may testify that they learned about drug risks from the medical literature, conferences, informal conversations with colleagues, and their own experience in using the product.[360] If, however, physicians do not become aware of such information from other sources, they may incorrectly interpret the absence of a warning on the label as providing some reassurance of the product's safety.[361] In addition, a manufacturer's over-promotion of a product may render an otherwise complete warning inadequate.[362]

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certain.'...Scientific studies suggesting associations between products and injuries may themselves be subjected to legitimate question as to the validity of their methods and the soundness of their conclusions.").

358. *Id.* at 1365 ("Evidence of a risk would be scientifically credible if the data upon which it is based, the methodology employed, and its conclusions identifying the existence of a risk comply with generally accepted scientific methodology and analysis."). In short, Justice Kennard sought to overlay rules for the admissibility of expert testimony on the question of when a risk becomes knowable. *See id.* at 1364 ("In determining the admissibility of new scientific techniques, this court has held that evidence of a technique is admissible only if it has gained acceptance in the particular scientific field to which it belongs.").

359. *See* Wheat v. Pfizer, Inc., 31 F.3d 340, 343 (5th Cir. 1994); Guevara v. Dorsey Labs., 845 F.2d 364, 367 (1st Cir. 1988); Plummer v. Lederle Labs., 819 F.2d 349, 358 (2d Cir. 1987); Kirsch v. Picker Int'l, Inc., 753 F.2d 670, 671 (8th Cir. 1985); Stanback v. Parke, Davis & Co., 657 F.2d 642, 645 (4th Cir. 1981); Spychala v. G.D. Searle & Co., 705 F. Supp. 1024, 1032 (D.N.J. 1988); Wooten v. Johnson & Johnson Prods., Inc., 635 F. Supp. 799, 803 (N.D. Ill. 1986).

360. *See, e.g.*, Goodson v. Searle Labs., 471 F. Supp. 546, 548 (D. Conn. 1978); Mampe v. Ayerst Labs., 548 A.2d 798, 802 (D.C. 1988); Felix v. Hoffman-LaRoche, Inc., 540 So. 2d 102, 105 (Fla. 1989); Wyeth Labs., Inc. v. Fortenberry, 530 So. 2d 688, 689, 691 (Miss. 1988); Glucksman v. Halsey Drug Co., 553 N.Y.S.2d 724, 726 (App. Div. 1990); Oppenheimer v. Sterling Drug, Inc., 219 N.E.2d 54, 58 (Ohio Ct. App. 1964); Stewart v. Janssen Pharmaceutica, Inc., 780 S.W.2d 910, 912 (Tex. Ct. App. 1989).

361. As one court explained

> Since pharmaceutical companies are bound by federal law to fulfill this duty, physicians are justified in relying on the literature from pharmaceutical companies to inform them...[and] are also justified in assuming that, in the absence of a warning from a pharmaceutical company about a particular drug, reasonable evidence of an association of serious adverse reactions and potential safety hazards with that particular drug does not yet exist.

Wells v. Armour Pharm. Co., 832 F. Supp. 1467, 1484 (M.D. Fla. 1993) (internal quotation marks omitted).

362. *See* Salmon v. Parke, Davis & Co., 520 F.2d 1359, 1363–64 (4th Cir. 1975); Globetti v. Sandoz Pharm. Corp., 2001 U.S. Dist. LEXIS 2093, at *8–9, 25–32 (N.D. Ala.

Sellers must communicate risk information through the most effective channels available. For instance, a number of courts have demanded the use of methods other than labeling to convey information to physicians about prescription drug risks, in part because physicians rarely see the actual product they have prescribed for any particular patient or bother to read the package insert.[363] Several courts have focused on the use of pharmaceutical company sales representatives to convey precautionary information about prescription drugs to physicians.[364] When "Dear Doctor" letters are circulated, the manufacturer may be held liable for not using sales representatives to convey the information.[365] One court credited evidence that the plaintiff's doctor "(and other general practitioners) receive so much literature on drugs that it is impossible to read all of it."[366] The

2001); Stevens v. Parke, Davis & Co., 507 P.2d 653, 661–62 (Cal. 1973); Holley v. Burroughs Wellcome Co., 348 S.E.2d 772, 777 (N.C. 1986); Incollingo v. Ewing, 282 A.2d 206, 220 (Pa. 1971); *cf.* Baldino v. Castagna, 478 A.2d 807, 812 (Pa. 1984) (holding that a jury could find for the manufacturer on allegations that its detail representatives had diluted the warnings by overpromoting a drug product). *See generally* Janet Fairchild, Annotation, *Promotional Efforts Directed Toward Prescribing Physician as Affecting Prescription Drug Manufacturer's Liability for Product-Caused Injury*, 94 A.L.R.3d 1080 (1979 & 2000 Supp.).

363. *See* Sterling Drug, Inc. v. Yarrow, 408 F.2d 978, 992 (8th Cir. 1969) ("[I]t was not unreasonable to find that the appellant should have employed all its usual means of communication...to warn the prescribing physicians of these dangers."); Finn v. G.D. Searle & Co., 677 P.2d 1147, 1169 n.20 (Cal. 1984) (Bird, C.J., dissenting) ("These include advertising and promotional literature, letters to the medical profession and oral communications by sales representatives."); Richards v. Upjohn Co., 625 P.2d 1192, 1196–97 (N.M. Ct. App. 1980); Baker v. St. Agnes Hosp., 421 N.Y.S.2d 81, 86 (App. Div. 1979) ("There are other, well-known methods by which pharmaceutical manufacturers apprise the medical profession of the dangers of a drug.").

364. *See* Yarrow v. Sterling Drug, Inc., 263 F. Supp. 159, 163 (D.S.D. 1967), *aff'd*, 408 F.2d 978, 990–94 (8th Cir. 1969) (holding a pharmaceutical company liable for failing to warn of newly discovered side effects, notwithstanding letters it had sent to physicians, because it had not used its sales representatives to convey the information); Mahr v. G.D. Searle & Co., 390 N.E.2d 1214, 1232 (Ill. App. Ct. 1979); *cf.* Wallace v. Upjohn Co., 535 So. 2d 1110, 1117 (La. Ct. App. 1988) (sales persons would not be personally liable for failing to warn physicians).

365. *See* Hoffman v. Sterling Drug, Inc., 485 F.2d 132, 146 (3d Cir. 1973) ("Nor was mailing drug literature to physicians necessarily an effective way to reach them....[T]he jury could reasonably have found that a considerable amount of such literature winds up in the wastebasket and is not adequate to advise doctors concerning matters of utmost importance."); *Yarrow*, 408 F.2d at 994 ("The trier of fact could reasonably conclude that the urgency of the circumstances reasonably required more than the relatively slow action and relative lack of emphasis employed in composing and circulating the 'Dear Doctor' letter."). Conversely, when companies do use their sales representatives to disseminate information about possible new side effects, some courts have criticized them for not sending a "Dear Doctor" letter instead. *See* Sterling Drug, Inc. v. Cornish, 370 F.2d 82, 84 (8th Cir. 1966); *Hoffman*, 485 F.2d at 146–47 (noting that "some doctors did not take the time to speak to detail men, some did not always accept the product cards or brochures offered, and some did not always listen to what the detail men said about a drug").

366. *Yarrow*, 408 F.2d at 990.

court recognized that health care professionals rely on a variety of channels of information and that a manufacturer's warning may reach the prescribing physician indirectly.[367] Thus, product labeling alone sometimes fails to satisfy the duty to warn.

Even if a manufacturer provides adequate risk information about a drug or device, physicians will decide whether or not to use the product based in part on the comparative risk-benefit profile of alternative treatments.[368] Because medical professionals frequently lack equally strong evidence about other interventions such as surgery,[369] drug labeling alone often will fail to clarify therapeutic choices. Courts have, however, declined to impose a duty on product sellers to educate health care providers about information that has appeared in the medical literature.[370]

A few commentators have recognized that overwarning of prescription drug side effects may adversely affect treatment decisions if other options (which fall outside of the products liability system) do not have to carry equally alarming risk information:

> [The FDA] has an interest in "rational prescribing," i.e., ensuring that the risks and benefits of a particular drug be fairly presented so

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367. *See id.* (noting that the evidence showed "that Dr. Olson relied on detail men, medical conventions, medical journals and conversations with other doctors for information on drugs"); *id.* at 994 ("[I]t could be inferred that a reasonably earlier warning, with greater intensity could well have reached [the plaintiff]'s physician directly, or indirectly through other professional channels such as conversations with other doctors and discussions at conventions.").

368. *See* James A. Henderson, Jr. & Aaron D. Twerski, *Drug Designs* Are *Different*, 111 YALE L.J. 151, 156 (2001) ("Indeed, that may be said to be the essence of the healer's craft–assessing and comparing all available courses of medical treatment."); *see also id.* at 174 (conceding that a "presumption of physician infallibility seems factually unrealistic").

369. *See supra* notes 329–30 and accompanying text; *see also* Aaron D. Twerski & Neil B. Cohen, *Comparing Medical Providers: A First Look at the New Era of Medical Statistics*, 58 BROOK. L. REV. 5, 8–9 (1992) ("When the provider has statistical risk information as to one form of medical intervention, but no such information as to alternative treatments, a simple comparison of risks is impossible.").

370. *See* May v. Dafoe, 611 P.2d 1275, 1277–78 (Wash. Ct. App. 1980) (distinguishing the seller of hospital equipment from drug manufacturers); *see also* Bernhardt v. Pfizer, Inc., No. 00 Civ. 4042 LMM, 2000 WL 1738645 (S.D.N.Y. 2000) (refusing to issue an injunction ordering a drug manufacturer to notify physicians about the results of a large RCT finding that its antihypertensive agent worked less well than diuretics because this presented an issue for the FDA to resolve); Demmler v. SmithKline Beecham Corp., 671 A.2d 1151, 1154–55 (Pa. Super. Ct. 1996) (rejecting an inadequate warning claim for failure to specify the appropriate therapy in the event that a listed side effect occurred); *cf.* Willet v. Baxter Int'l, Inc., 929 F.2d 1094, 1099 (5th Cir. 1991) (holding that the plaintiff could not prove causation when the manufacturer of a replacement heart valve had neglected to warn of a 0.03 percent risk of failure because the implant surgeon had decided to proceed with the operation in spite of a four percent risk of failure from other factors).

> that a physician can compare them with other available therapies. That goal is not advanced if a drug is made to appear riskier than other drugs and other therapies due to the over-dramatization of risk information. To allow a warning based on inconclusive evidence or scientific hunches results in doctors not prescribing effective drugs to a patient because of the erroneous belief that a side-effect might occur.[371]

Alternatively, physicians may tune out if overwhelmed with risk information.[372] In either case, the result may be suboptimal treatment choices.

2. Medical Malpractice

Traditionally, courts treated custom among practitioners as defining the standard of care in medical malpractice cases,[373] so a jury could not impose liability against a physician who followed the applicable custom. For over a century, courts have framed the medical malpractice inquiry by reference to the knowledge, skill and judgment of other practitioners.[374] Thus, unlike most other tortfeasors, medical professionals effectively set the standard of care against which

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371. Feldman v. Lederle Labs., 592 A.2d 1176, 1200 (N.J. 1991) (Garibaldi, J., dissenting); *see also* Richard M. Cooper, *Drug Labeling and Products Liability: The Role of the Food and Drug Administration*, 41 FOOD DRUG COSM. L.J. 233, 238 (1986) ("This point has additional force where there is no similar collection of risk information about alternative therapies, such as surgical procedures."); Thomas Scarlett, *The Relationship Among Adverse Drug Reaction Reporting, Drug Labeling, Product Liability, and Federal Preemption*, 46 FOOD DRUG COSM. L.J. 31, 36 (1991) ("[O]verstated warnings could tip the judgment of the medical profession in an undesirable direction.").

372. *See* Carlin v. Superior Court, 920 P.2d 1347, 1361 (Cal. 1996) (Kenard, J., concurring in part and dissenting in part) ("[E]ven physicians...may be overwhelmed by excessive warnings."); *see also* Thomas v. Hoffman-LaRoche, 949 F.2d 806, 816 n.40 (5th Cir. 1992) (noting that the imposition of liability for failure to warn about reported but unconfirmed adverse experiences with prescription medications could "force drug manufacturers to list, and perhaps contraindicate, every possible risk in order to avoid the possibility of liability"); *id.* ("If manufacturers so respond to the possibility of liability, physicians will begin to ignore or discount the warnings provided by the drug manufacturers. Permitting a jury to find liability on such a basis would undermine the important role of warnings as a device to communicate vital information to physicians."); Lars Noah, *The Imperative to Warn: Disentangling the "Right to Know" from the "Need to Know" About Consumer Product Hazards*, 11 YALE J. ON REG. 293, 382–83 (1994) ("In the event that labeling included warnings of all possible side effects, the cacophony of risk information could undermine a doctor's ability to appreciate warnings about meaningful hazards.").

373. *See* RESTATEMENT (SECOND) OF TORTS § 299A (1965); *see also* Theodore Silver, *One Hundred Years of Harmful Error: The Historical Jurisprudence of Medical Malpractice*, 1992 WIS. L. REV. 1193, 1212–19 (criticizing this formulation).

374. *See* Pike v. Honsinger, 49 N.E. 760, 762 (N.Y. 1898) ("The law holds [a physician] liable for an injury to his patient resulting from want of the requisite knowledge and skill, or the omission to exercise reasonable care, or the failure to use his best judgment.").

courts would judge their performance. Indeed, courts held doctors only to the custom in their locality on the theory that rural practitioners would have access to more limited resources–including information and the opportunities to learn from direct and indirect experience–than their colleagues in urban centers.[375] With changes in the acquisition of medical knowledge, many jurisdictions moved away from the locality rule.[376] As one court explained (two decades before the Internet became popular): "Scientific information flows freely among medical institutions throughout the country. Professional journals and numerous other networks of continuing education are all national in scope."[377] In particular, many courts now hold board-certified specialists to a national standard of care.[378]

Even with the shift to a national standard of care, the courts continued to defer to custom. They did not appear to care whether the customary practice in fact worked,[379] or whether newly emerging research cast some doubt on the existing practice,[380] trusting the medical community to sort out such questions.[381]

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375. *See* Robbins v. Footer, 553 F.2d 123, 127–28 (D.C. Cir. 1977) ("The courts generally assumed that the rural practitioner had less access to the latest medical information and facilities than urban doctors and did not have the benefit of the same breadth of experience.").

376. *See* Logan v. Greenwich Hosp. Ass'n, 465 A.2d 294, 304–05 (Conn. 1983); McDaniel v. Hendrix, 401 S.E.2d 260, 262 (Ga. 1991); Brune v. Belinkoff, 235 N.E.2d 793, 798 (Mass. 1968) ("The time has come when the medical profession should no longer be Balkanized by the application of varying geographic standards in malpractice cases."); Hall v. Hilbun, 466 So. 2d 856, 868–73 (Miss. 1985); Chapel v. Allison, 785 P.2d 204, 207–10 (Mont. 1990); Sheeley v. Mem. Hosp., 710 A.2d 161, 165–67 (R.I. 1998); James O. Pearson, Jr., Annotation, *Modern Status of "Locality Rule" in Malpractice Action Against Physician Who Is Not a Specialist*, 99 A.L.R.3d 1133, 1139 (1980).

377. *Robbins*, 553 F.2d at 128 (adding that the continuing validity of the assumption about differential access to information "in our age of ubiquitous national communication networks both within and without the medical profession is extremely doubtful"); *see also* Shilkret v. Annapolis Emergency Hosp. Ass'n, 349 A.2d 245, 252 (Md. 1975) (same); Douglas v. Bussabarger, 438 P.2d 829, 837 (Wash. 1968) ("Modern means of transportation permit country doctors to attend up-to-date medical seminars; [and] the general circulation of medical journals makes new developments readily available to them...."); Jon R. Waltz, *The Rise and Gradual Fall of the Locality Rule in Medical Malpractice Litigation*, 18 DEPAUL L. REV. 408, 413–14 (1969) ("The proliferation of medical literature, attendance at seminars and conferences, and reasonably speedy mail service enhances and updates the knowledge of practitioners in small communities as well as large.").

378. *See* Bruni v. Tatsumi, 346 N.E.2d 673, 679 (Ohio 1976); Jay M. Zitter, Annotation, *Standard of Care Owed to Patient by Medical Specialist as Determined by Local, "Like Community," State, National, or Other Standards*, 18 A.L.R.4th 603, 607, 614–19 (1982).

379. *See* Schneider v. Revici, 817 F.2d 987, 990 (2d Cir. 1987) ("[T]he issue in medical malpractice is not whether a particular treatment is effective but whether that treatment is a deviation from accepted medical practice in the community.").

380. *See* Osborn v. Irwin Mem. Blood Bank, 7 Cal. Rptr. 2d 101, 123, 127–28 (Ct. App. 1992); *see also* Joseph H. King, Jr., *In Search of a Standard of Care for the Medical Profession: The "Accepted Practice" Formula*, 28 VAND. L. REV. 1213, 1244 (1975) ("[T]he strict customary practice rule appears incompatible with a rapidly changing

Where custom may have varied, physicians would not have to fear malpractice judgments if they abided by the practice of a respectable minority of practitioners.[382] conversely, a departure from the prevailing medical custom would amount to strong evidence of malpractice.

Although this tradition of complete judicial deference to medical custom may be waning,[383] adherence (or non-adherence) to customary medical practice will continue to play a significant role in the resolution of most malpractice lawsuits. Of course, the occasions for physician negligence increase along with advances in knowledge and technology.[384] In addition, the proliferation of new

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science and may glorify medical custom without due regard for advances in the state of the art.").

381. *See* Doe v. Am. Red Cross Blood Servs., 377 S.E.2d 323, 326 (S.C. 1989) (deferring "to the collective wisdom of a profession, such as physicians"); W. PAGE KEETON ET AL., PROSSER AND KEETON ON THE LAW OF TORTS § 32, at 189 (5th ed. 1984) (explaining the rule of deference to custom as reflecting "the healthy respect which the courts have had for the learning of a fellow profession, and their reluctance to overburden it with liability based on uneducated judgment").

382. *See* Chumbler v. McClure, 505 F.2d 489, 492 (6th Cir. 1974); Smith v. Lerner, 387 N.W.2d 576, 580–82 (Iowa 1986); Jones v. Chidester, 610 A.2d 964, 969 (Pa. 1992) ("Where competent medical authority is divided, a physician will not be held responsible if in the exercise of his judgment he followed a course of treatment advocated by a considerable number of recognized and respected professionals in his given area of expertise."); *see also* Gala v. Hamilton, 715 A.2d 1108, 1110–15 (Pa. 1998) (rejecting the argument that the respectable minority position had to find support in the medical literature); RESTATEMENT (SECOND) OF TORTS § 299A cmt. f (1965) ("The law cannot undertake to decide technical questions of proper practice over which experts reasonably disagree....").

383. *See* Philip G. Peters, Jr., *The Quiet Demise of Deference to Custom: Malpractice Law at the Millennium*, 57 WASH. & LEE L. REV. 163, 188 (2000). Only rarely, however, do courts decide that a particular medical custom is suboptimal. *See* Helling v. Carey, 519 P.2d 981, 983 (Wash. 1974) (glaucoma screening); *see also* United Blood Servs. v. Quintana, 827 P.2d 509, 520–21, 524–26 (Colo. 1992) (holding that a jury should have decided whether professional standards for screening blood for AIDS were inadequate); Burton v. Brooklyn Doctors Hosp., 452 N.Y.S.2d 875, 879–80 (App. Div. 1982); Toth v. Cmty. Hosp., 239 N.E.2d 368, 373 (N.Y. 1968) (allowing a claim against a physician who knew from published research that customary practice entailed a serious risk of injury); Hood v. Phillips, 554 S.W.2d 160, 165 (Tex. 1977) (rejecting the "incorrect notion that the standard for malpractice is to be determined by a poll of the medical profession"); *id.* at 166 (holding that the trial judge erred by not submitting a negligence claim to the jury where "there was expert medical testimony characterizing carotid surgery as an unaccepted mode of treatment for emphysema, as a controversial procedure, as a procedure not supported by medical evidence, and as a surgical procedure which has been tried by a number of physicians, found ineffectual, and abandoned"); Nowatske v. Osterloh, 543 N.W.2d 265, 273 (Wis. 1996).

384. *See* Mark F. Grady, *Why Are People Negligent? Technology, Nondurable Precautions, and the Medical Malpractice Explosion*, 82 NW. U. L. REV. 293, 298–99, 330–31 (1988); *id.* at 312 ("[W]ith the advent of dialysis, there are many compliance opportunities and when someone forgets to test a solution or check a shunt and harm results, there is a negligence claim that could not have existed before dialysis technology

technologies threatens to fragment the shared knowledge-base required for the formation of stable customs.[385] To some extent, existing networks for the exchange of information help to counteract this tendency,[386] but the dramatic expansion of biomedical knowledge may complicate the resolution of such disputes.[387]

Similar issues arise in connection with disputes over health insurance coverage of new technologies insofar as courts use a general acceptance standard in deciding whether a procedure remains experimental.[388] In some instances,

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was introduced."); Martin J. Hatlie, Editorial, *Climbing 'The Learning Curve': New Technologies, Emerging Obligations*, 270 JAMA 1364, 1365 (1993) ("The difficulty with rapidly emerging treatment modalities is that a 'customary practice' may not yet exist."); Brian Kibble-Smith & Arthur W. Hafner, *The Effect of the Information Age on Physicians' Professional Liability*, 36 DEPAUL L. REV. 69, 86 (1986) ("The physician's duty to keep abreast will be revised as information management technology continues to affect information distribution and access."); Donald E. Kacmar, Note, *The Impact of Computerized Medical Literature Databases on Medical Malpractice Litigation: Time for Another* Helling v. Carey *Wake-up Call?*, 58 OHIO ST. L.J. 617, 644–48 (1997); Margaret Lent, Note, *The Medical and Legal Risks of the Electronic Fetal Monitor*, 51 STAN. L. REV. 807, 828 (1999) (explaining that "several courts have indicated that a physician has a specific duty to 'keep abreast of progress,'" which "obligate[s] physicians to read, interpret, and apply the latest research regarding the drugs, techniques, and procedures employed in their specialties"); *id.* at 831–32 (adding that RCTs have cast doubt on the customary use of electronic fetal monitoring); Edward A. Marshall, Note, *Medical Malpractice in the New Eugenics: Relying on Innovative Tort Doctrine to Provide Relief When Gene Therapy Fails*, 35 GA. L. REV. 1277, 1304–07 (2001).

385. *See* James A. Henderson, Jr. & John A. Siliciano, *Universal Health Care and the Continued Reliance on Custom in Determining Medical Malpractice*, 79 CORNELL L. REV. 1382, 1389–91 & n.32 (1994). "New technologies represent new ideas that take time to absorb and master, thus undermining the kind of informational homogeneity that permits custom formation." *Id.* at 1391; *see also id.* at 1386 (If an "activity is besieged by constant change and innovation, a shared base of understanding can easily erode as some participants lag behind others in their ability to keep abreast of new developments.").

386. *See id.* at 1391 ("[A] common professional training, ongoing education, and professional journals help bolster the necessary homogeneity of knowledge. For example, the *New England Journal of Medicine* is a good antidote to the destabilizing impact of relentless technological innovation.").

387. *See* Finder, *supra* note 216, at 88 ("[W]hat is customary practice constantly evolves in a world where medical technology advances exponentially."); Rosoff, *supra* note 198, at 334 ("[T]he court's job in managing health care litigation may be significantly more complex in the face of the better knowledge and evidence that EBM makes possible than it would have been previously in 'less enlightened' times.").

388. *See, e.g.*, Miller v. Whitburn, 10 F.3d 1315, 1320 (7th Cir. 1993); Holder v. Prudential Ins. Co., 951 F.2d 89, 90–91 (5th Cir. 1992); Goodman v. Sullivan, 891 F.2d 449, 451 (2d Cir. 1989); Weaver v. Reagan, 886 F.2d 194, 198–99 (8th Cir. 1989); *see also* Sharona Hoffman, *A Proposal for Federal Legislation to Address Health Insurance Coverage for Experimental and Investigational Treatments*, 78 OR. L. REV. 203, 220 (1999); *cf.* Schumake v. Travelers Ins. Co., 383 N.W.2d 259, 264 (Mich. Ct. App. 1985) ("[S]ince medicine is an evolving science in which treatments are at one time regarded as valid and later discredited, we hold that a decision as to necessity shall be reviewed in light of knowledge which existed at the time the [treatment] decision was rendered."); *id.* at 265 n.3 ("[I]t is reasonable to assume that there would be some time lag between publication of

physicians may adopt innovative treatments without having any real evidence, but some courts decide in favor of patients who seek insurance coverage if the new procedure or technology attracts a sufficiently wide following.[389] In other cases, physicians may fail to adopt new technologies as rapidly as the available evidence would justify, which may result in coverage denials for effective treatments.[390]

Normally, parties have to introduce expert testimony in order to identify customary medical practice.[391] Litigants also may call on physicians to testify on questions of causation in malpractice and other cases. The Federal Rules of Evidence include a "learned treatise" exception to the rule against admission of hearsay evidence, allowing courts to admit "statements contained in published treatises, periodicals or pamphlets on a subject of...medicine, or other science."[392] Although normally applied to authoritative textbooks and treatises, some courts have allowed use of the exception to admit published scientific articles.[393] The exception exists because "a high standard of accuracy is engendered by various factors: the treatise is written primarily and impartially for professionals, subject to scrutiny and exposure for inaccuracy, with the reputation of the writer at stake."[394] As discussed previously, one may quibble with the accuracy of these assumptions.

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new research findings in professional journals and the time when such findings would become part of the informational base available to practicing physicians.").

389. *See* John H. Ferguson et al., *Court-Ordered Reimbursement for Unproven Medical Technology: Circumventing Technology Assessment*, 269 JAMA 2116, 2120 (1993); E. Haavi Morreim, *From the Clinics to the Courts: The Role Evidence Should Play in Litigating Medical Care*, 26 J. HEALTH POL., POL'Y & L. 409, 411–13 (2001) (describing litigation over high-dose chemotherapy followed by autologous bone marrow transplant (HDC/ABMT) for breast cancer patients, which later proved to be ineffective).

390. *See* Richard S. Saver, Note, *Reimbursing New Technologies: Why Are the Courts Judging Experimental Medicine?*, 44 STAN. L. REV. 1095, 1107–08, 1125 (1992).

391. *See* Cox v. Dela Cruz, 406 A.2d 620, 622 (Me. 1979); Harris v. Robert C. Groth, M.D., Inc., 663 P.2d 113, 118–19 (Wash. 1983); Vassos v. Roussalis, 658 P.2d 1284, 1288 (Wyo. 1983).

392. FED. R. EVID. 803(18).

393. *See, e.g.*, Ward v. United States, 838 F.2d 182, 187 (6th Cir. 1988); Tart v. McGann, 697 F.2d 75, 77–78 (2d Cir. 1982); *cf.* Meschino v. N. Am. Drager, Inc., 841 F.2d 429, 434 (1st Cir. 1988) (upholding decision against admission of articles that had not been established as authoritative, observing that "an article does not reach the dignity of a 'reliable authority' merely because some editor, even a most respectable one, sees fit to circulate it"); Dartez v. Fiberboard Corp., 765 F.2d 456, 465 (5th Cir. 1985) (holding that the admission of medical journal articles was improper because expert did not testify about them); Ellis v. Int'l Playtex, Inc., 745 F.2d 292, 305–06 (4th Cir. 1984) (barring the use of an article that was not relevant to the plaintiff's condition); Conde v. Velsicol Chem. Corp., 804 F. Supp. 972, 990 (S.D. Ohio 1992) (same), *aff'd*, 24 F.3d 809 (6th Cir. 1994).

394. FED. R. EVID. 803(18) advisory committee's note; *see also* United States v. Jones, 712 F.2d 115, 121 (5th Cir. 1983) (explaining that the exception is "confined to published works that have been subjected to widespread collegial scrutiny"); Jacober v. St. Peter's Med. Ctr., 608 A.2d 304, 315 (N.J. 1992) ("[A]n opinion must ordinarily satisfy a certain level of reliability in order to find its way into publication, and once published, a text is open to ongoing scrutiny, criticism, and revision by other members of that discipline."); JOHN HENRY WIGMORE, A TREATISE ON THE ANGLO-AMERICAN SYSTEM OF

In some respects, package inserts for prescription drugs closely resemble clinical practice guidelines.[395] Although such labeling typically focuses on just a subset of all uses of a particular product rather than the whole range of options for treating a particular condition, and it may lag behind the latest research (notwithstanding the unforgiving knowability standard used to trigger a manufacturer's tort duty to warn),[396] the package insert provides detailed guidance about appropriate uses and potential risks. Indeed, if phrased as a "contraindication," precautionary information would effectively amount to a direction to the physician never to use the drug in those circumstances.[397]

Nonetheless, courts have struggled in determining the appropriate status of such labeling.[398] In some jurisdictions, the package insert may serve as prima facie evidence of the applicable standard of care;[399] in other jurisdictions, it may provide only some relevant evidence about the standard of care;[400] and, in a few jurisdictions, the package insert amounts to inadmissible hearsay.[401] In issuing

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EVIDENCE IN TRIALS AT COMMON LAW § 1692(b) (3d ed. 1940) ("The writer of a learned treatise publishes primarily for his profession. He knows that every conclusion will be subjected to careful professional criticism, and is open ultimately to certain refutation if not well-founded....").

395. *See* Boyd v. Louisiana Med. Mut. Ins. Co., 593 So. 2d 427, 429–30 (La. Ct. App. 1991).

396. *See* Weaver v. Reagan, 886 F.2d 194, 198–99 (8th Cir. 1989). In one case, a physician defending against a malpractice claim for exceeding the manufacturer's recommended dose sought to introduce an editorial from a medical journal explaining that best medical practice often requires disregarding prescription drug labeling. *See* O'Brien v. Angley, 407 N.E.2d 490, 492–94 (Ohio 1980) (holding that the trial judge erred in admitting this editorial into evidence).

397. *See* Richardson v. Miller, 44 S.W.3d 1, 8 n.2, 16–17 (Tenn. Ct. App. 2000) (holding that the trial judge had erred in excluding label that had specifically warned against the off-label use selected by the physician); *see also* James R. Bird, Comment, *Package Inserts for Prescription Drugs as Evidence in Medical Malpractice Suits*, 44 U. CHI. L. REV. 398, 436–37 (1977) (arguing that courts should differentiate between the categories of information and give contraindications the greatest weight); *cf.* Young v. Cerniak, 467 N.E.2d 1045, 1057–58 (Ill. App. Ct. 1984) ("[W]e are aware of no case which holds that a drug manufacturer's recommendation regarding dosage, unaccompanied by any warning of adverse consequences if the recommendation is not followed, is proof of the standard of care.").

398. *See* David Carl Minneman, Annotation, *Medical Malpractice: Drug Manufacturer's Package Insert Recommendations as Evidence of Standard of Care*, 82 A.L.R.4th 166 (1990 & 2000 Supp.).

399. *See, e.g.*, Julien v. Barker, 272 P.2d 718, 724 (Idaho 1954); Fournet v. Roule-Graham, 783 So. 2d 439, 442–44 (La. Ct. App. 2001); Mulder v. Parke Davis & Co., 181 N.W.2d 882, 887 (Minn. 1970); Thompson v. Carter, 518 So. 2d 609, 612–13 (Miss. 1987); Paul v. Boschenstein, 482 N.Y.S.2d 870, 871 (App. Div. 1984).

400. *See, e.g.*, Salgo v. Leland Stanford Jr. Univ., 317 P.2d 170, 180 (Cal. Ct. App. 1957); Mozer v. Kerth, 586 N.E.2d 759, 763–64 (Ill. App. Ct. 1992); Bissett v. Renna, 710 A.2d 404, 407–08 (N.H. 1998); Morlino v. Med. Ctr., 706 A.2d 721, 729–30 (N.J. 1998); Ramon v. Farr, 770 P.2d 131, 134–35 (Utah 1989).

401. *See, e.g.*, Rosario v. New York City Health & Hosps. Corp., 450 N.Y.S.2d 805, 807 (App. Div. 1982).

regulations, the FDA has attempted to assuage concerns that its drug labeling decisions would impact medical malpractice litigation,[402] but it makes little sense for the courts to disregard what may be the most evidence-based of all practice guidelines just because doctors habitually ignore them.[403]

To the extent that the medical community can reduce customs to writing and perhaps also receive the endorsement of respected organizations, it may reduce the risk that judges and juries will decide to second-guess choices made by health care professionals.[404] Courts have allowed plaintiffs to introduce clinical practice guidelines as inculpatory evidence where physicians have deviated from those recommendations,[405] and they have allowed defendants to make use of practice guidelines as exculpatory evidence.[406] In at least two cases the parties engaged in a battle of the guidelines where different organizations had made conflicting recommendations about the appropriate frequency for breast cancer screening.[407] Legislatures in a few states have made adherence to clinical practice

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402. *See* 44 Fed. Reg. 37,434, 37,435 (June 26, 1979); 43 Fed. Reg. 4214, 4214–15 (Jan. 31, 1978).

403. *See* Vicki E. Lawrence, *Drug Manufacturers' Recommendations and the Common Knowledge Rule to Establish Medical Malpractice*, 63 NEB. L. REV. 859, 875 (1984) ("[I]t is simply unacceptable to allow the manufacturer's recommendation to be ignored on the rationale that it is customarily disregarded by physicians, in light of the fact that the usage and dosage instructions must be supported by sufficient scientific proof in order to receive FDA approval.").

404. *See* Troyen A. Brennan, *Practice Guidelines and Malpractice Litigation: Collision or Cohesion?*, 16 J. HEALTH POL., POL'Y & L. 67, 68 (1991) ("[G]uidelines should act as useful inculpatory or exculpatory evidence of the standard of care."); *id.* at 74, 76 (analogizing guidelines to review articles used as the foundation of an expert's testimony, and adding that, "since they are endorsed by prestigious groups in many circumstances, practice guidelines will be very influential"); Mark A. Hall, *The Defensive Effect of Medical Practice Policies in Malpractice Litigation*, LAW & CONTEMP. PROBS., Spring 1991, at 119, 129–45; Eleanor D. Kinney & Marilyn M. Wilder, *Medical Standard Setting in the Current Malpractice Environment: Problems and Possibilities*, 22 U.C. DAVIS L. REV. 421, 449–50 (1989); Richard E. Leahy, Comment, *Rational Health Policy and the Legal Standard of Care: A Call for Judicial Deference to Medical Practice Guidelines*, 77 CAL. L. REV. 1483, 1506–08 (1989); *id.* at 1509–19 (rebutting some of the criticisms directed against the use of practice guidelines in litigation).

405. *See, e.g.*, James v. Woolley, 523 So. 2d 110, 112 (Ala. 1988); Pollard v. Goldsmith, 572 P.2d 1201, 1203 (Ariz. Ct. App. 1977); Nelson v. Hammon, 802 P.2d 452, 454–57 (Colo. 1990); Washington v. Washington Hosp. Ctr., 579 A.2d 177, 182 (D.C. 1990); Williams v. Lallie Kemp Charity Hosp., 428 So. 2d 1000, 1005 (La. Ct. App. 1983); Monusko v. Postle, 437 N.W.2d 367, 368 (Mich. Ct. App. 1989); Birchfield v. Texarkana Mem. Hosp., 747 S.W.2d 361, 364 (Tex. 1988).

406. *See, e.g.*, Moore v. Baker, 989 F.2d 1129, 1133 & n.2 (11th Cir. 1993); Parker v. Southwest La. Hosp. Ass'n, 540 So. 2d 1270, 1274 (La. Ct. App. 1989).

407. *See* Kramer v. Milner, 639 N.E.2d 157, 158–59 (Ill. App. Ct. 1994); Levine v. Rosen, 616 A.2d 623, 628 (Pa. 1993); *see also* Mark Crane, *Clinical Guidelines: A Malpractice Safety Net?*, MED. ECON., Apr. 12, 1999, at 236, 239–40; Nancy Volkers, *NCI Replaces Guidelines with Statement of Evidence*, 86 J. NAT'L CANCER INST. 14 (1994).

guidelines a conclusive defense to tort liability.[408] Although it seems unwise to treat such guidelines as definitive on questions of physician negligence, especially given the many limitations discussed previously, they can provide valuable additional evidence about the standard of care to which physicians should aspire.[409] Whatever role they may play in malpractice litigation, health care professionals might have greater incentives to abide by practice guidelines if they know that courts will admit such guidelines into evidence.[410]

In order for the threat of medical malpractice litigation to promote genuine EBM, however, the courts will have to do more than simply latch on to clinical practice guidelines. Although rarely litigated, courts do insist that physicians keep abreast of the latest clinically-relevant research in their fields,[411] in effect demanding adherence to the state-of-the-art rather than simply existing custom. As true in products liability cases, courts do not demand that physicians take into account unknowable information,[412] but the failure to conduct a literature search may provide the basis for a malpractice claim.[413]

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408. *See* Jennifer Begel, *Maine Physician Practice Guidelines: Implications for Medical Malpractice Litigation*, 47 ME. L. REV. 69, 76–88 (1995).

409. *See* Michelle M. Mello, *Of Swords and Shields: The Role of Clinical Practice Guidelines in Medical Malpractice Litigation*, 149 U. PA. L. REV. 645, 708–10 (2001); Rosoff, *supra* note 187, at 377–91; Sheila R. Shulman, *Clinical Practice Guidelines and Malpractice Law: An Evolving Standard of Care*, 46 FOOD DRUG COSM. L.J. 97, 105–06 (1991); *see also* Lowry v. Henry Mayo Newhall Mem. Hosp., 229 Cal. Rptr. 620, 624–25 (Ct. App. 1986) (holding that the selection of a drug different from that called for by American Heart Association guidelines for CPR did not demonstrate bad faith as required for bringing a malpractice claim under the state's "good samaritan" statute); Jewett v. Our Lady of Mercy Hosp., 612 N.E.2d 724, 726–27 (Ohio Ct. App. 1992) (holding that obstetrician's adherence to guidelines did not conclusively establish non-negligence).

410. *See* Andrew L. Hyams et al., *Medical Practice Guidelines in Malpractice Litigation: An Early Retrospective*, 21 J. HEALTH POL., POL'Y & L. 289, 310 (1996).

411. *See* Burton v. Brooklyn Doctors Hosp., 452 N.Y.S.2d 875, 879–80 (App. Div. 1982); Nowatske v. Osterloh, 543 N.W.2d 265, 273 (Wis. 1996) ("[A] reasonably competent practitioner is one who keeps up with advances in medical knowledge."); Angela Roddey Holder, *Failure to "Keep Up" as Negligence*, 224 JAMA 1461, 1462 (1973) ("Very few decisions have dealt with the sole question of whether or not a physician has been negligent simply because he did not use the latest methods of treatment. Those that have, however, apparently find a positive obligation to 'keep up' included in the applicable standard of care.").

412. *See* Klisch v. MeritCare Med. Group, Inc., 134 F.3d 1356, 1359 (8th Cir. 1998); Mallett v. Pirkey, 466 P.2d 466, 470 (Colo. 1970); Tanuz v. Carlberg, 921 P.2d 309, 315 (N.M. Ct. App. 1996) ("[A]lthough there was mounting evidence against the safety of the Vitek [TMJ] implants during the 1980s, it was not known until the safety alerts were issued [by the manufacturer and the FDA] that the Proplast material itself was to blame."); *see also* Pauscher v. Iowa Methodist Med. Ctr., 408 N.W.2d 355, 360 (Iowa 1987) (noting that a physician does not breach the duty to secure informed consent for failing to disclose an unknowable risk); Harnish v. Children's Hosp. Med. Ctr., 439 N.E.2d 240, 243 (Mass. 1982) (same); Frances H. Miller, *Health Care Information Technology and Informed Consent: Computers and the Doctor-Patient Relationship*, 31 IND. L. REV. 1019, 1032–36,

In addition, the possibility that courts might allow negligence claims to proceed against organizations involved in the formulation of clinical practice guidelines,[414] disclaimers notwithstanding, may create incentives to ensure that they formulate defensible recommendations, though one cannot ignore the countervailing risk that such a threat will discourage guideline development altogether. A few state courts have allowed tort claims to proceed against the American Association of Blood Banks for failing to recommend to its members certain screening procedures designed to prevent the use of HIV-infected blood,[415] and one federal court allowed claims to proceed against the National Hemophilia Foundation for publishing some allegedly inaccurate information about blood factor concentrates intended for distribution to patients.[416] A few commentators have argued that injured patients should get to assert similar claims against

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1041–42 (1998); Schuck, *supra* note 21, at 929 ("[T]he uncertainty surrounding many treatments means that even physicians are not omniscient about treatment risks....").

413. *See* Harbeson v. Parke Davis, Inc., 746 F.2d 517, 521, 525 (9th Cir. 1984) (holding, on an informed consent claim, that the doctors should have disclosed a drug's risk of causing birth defects based on an article previously published in a prominent British medical journal and other available literature). This form of negligence arises more frequently in attorney malpractice cases. *See* Lawrence Duncan MacLachlan, *Gandy Dancers on the Web: How the Internet Has Raised the Bar on Lawyers' Professional Responsibility to Research and Know the Law*, 13 GEO. J. LEGAL ETHICS 607, 614–26 (2000).

414. *See* Brennan, *supra* note 404, at 78–81; Rosoff, *supra* note 187, at 391–93. In addition, courts might not hesitate to impose tort liability on suppliers of medical "expert systems" that incorporate faulty practice guidelines into computerized decisionmaking products used by physicians. *See* Brian H. Lamkin, Comment, *Medical Expert Systems and Publisher Liability: A Cross-Contextual Analysis*, 43 EMORY L.J. 731 (1994).

415. *See* Snyder v. Am. Ass'n of Blood Banks, 676 A.2d 1036, 1048–50, 1055 (N.J. 1996) ("Playing a vital role in the protection of health, these [professional] associations are inescapably imbued with a public interest. The associations' commitment to public health should not immunize them from liability for the negligent discharge of their obligations."); Weigand v. Univ. Hosp. of NYU Med. Ctr., 659 N.Y.S.2d 395, 398–401 (Sup. Ct. 1997). *But see* N.N.V. v. Am. Ass'n of Blood Banks, 89 Cal. Rptr. 2d 885, 909 (Ct. App. 1999) (rejecting such a claim because "deference should be given to professional associations that are making these sorts of policy decisions based on evolving medical and scientific knowledge").

416. *See In re* Factor VIII or IX Concentrate Blood Prods. Litig., 25 F. Supp. 2d 837, 845, 848 (N.D. Ill. 1998). *But cf.* Cali v. Danek Med., Inc., 24 F. Supp. 2d 941, 949–50 (W.D. Wis. 1998) (rejecting fraud claims against medical societies for sponsoring seminars at which allegedly unsafe uses of pedicle screws in spinal fusion were discussed); Jones v. J.B. Lippincott Co., 694 F. Supp. 1216, 1217 (D. Md. 1988) (dismissing products liability claim against the publisher of a medical textbook); Bailey v. Huggins Diagnostic & Rehab. Ctr., Inc., 952 P.2d 768, 770–73 (Colo. Ct. App. 1997) (rejecting tort claims against the author of a book that exaggerated the risks associated with mercury in dental amalgam); Roman v. City of New York, 442 N.Y.S.2d 945, 947–48 (Sup. Ct. 1981) (rejecting tort claims against Planned Parenthood for a misstatement in a pamphlet about the effectiveness of tubal ligation).

medical societies responsible for drafting clinical practice guidelines.[417] Courts have, however, dismissed recent class action lawsuits alleging that the American Psychiatric Association conspired with the manufacturer of the drug product Ritalin® (methylphenidate hydrochloride) to include attention deficit hyperactivity disorder in the latest edition of its influential diagnostic guide (*DSM-IV*).[418]

V. CONCLUSION

In just over a decade, the EBM movement has received a great deal of attention in the health care community. It aspires to transform medical practice by urging physicians to draw on rigorous studies rather than simply rely on anecdotal experience. Even if it fails to attract a large number of adherents, or to fundamentally change medicine's epistemology, EBM has usefully encouraged medical professionals to become more reflective about the foundations for their treatment choices. In contrast, the call for evidence-based medicine has gone largely unnoticed outside of the health care community, even though it may offer important insights for other decisionmakers. Conversely, proponents of EBM may not have taken a sufficiently skeptical view of the biomedical literature and could benefit from the more critical perspectives of institutions external to the research enterprise. As importantly, perhaps, EBM reveals serious inadequacies in existing medical practice that deserve greater attention from regulatory agencies and the courts. A more realistic appreciation of the informational challenges faced by physicians should lead to improved doctrinal choices and, to the extent that these influence medical practice, superior treatment outcomes for patients.

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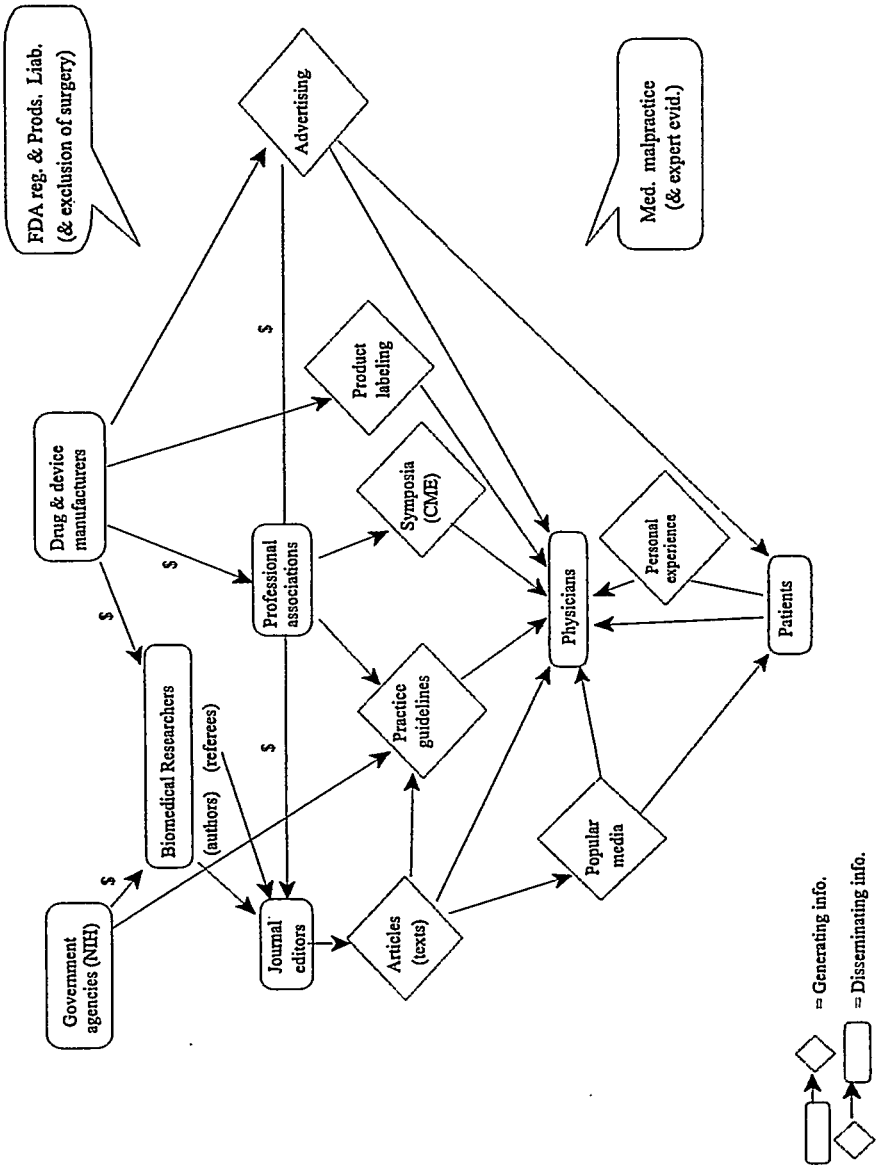
417. *See* Matthew R. Giannetti, Note, *Circumcision and the American Academy of Pediatrics: Should Scientific Misconduct Result in Trade Association Liability?*, 85 IOWA L. REV. 1507, 1546–66 (2000); *id.* at 1555 (explaining that pediatricians would foreseeably rely on practice guidelines because they would not typically undertake a review of the available medical literature); Megan L. Sheetz, Note, *Toward Controlled Clinical Care Through Clinical Practice Guidelines: The Legal Liability for Developers and Issuers of Clinical Pathways*, 63 BROOK. L. REV. 1341, 1357–77 (1997) (focusing on the development and use of guidelines by managed care organizations); *see also* Lars Noah, *Authors, Publishers, and Products Liability: Remedies for Defective Information in Books*, 77 OR. L. REV. 1195, 1203–18 (1998) (discussing tort theories available against providers of faulty information).

418. *See* Vess v. Ciba-Geigy Corp., No. Civ. 00CV1839B (CGA), 2001 WL 290333 (S.D. Cal. 2001); Hernandez v. Ciba-Geigy Corp., 200 F.R.D. 285 (S.D. Tex. 2001). The complaints echo objections that others have made about drug industry lobbying in connection with the drafting of recent editions of the *DSM*. *See* Noah, *supra* note 202, at 293–95.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