Of all the specialties in medicine, pathology, particularly diagnostic anatomical pathology, has been relatively slow in embracing the practice and principles of evidence-based medicine (EBM). Two reasons for this are as follows. First, pathology has been regarded for a long time as “the evidence” with respect to clinical inference. The classic clinico-pathological-correlation would finish with the pathologist lifting the veil from the hidden truth and providing the last word, often followed by a scholarly discussion of the science behind the disease. Second, pathologists involved in clinical care – particularly surgical pathologists – are expected to render a clear-cut diagnosis that will provide the basis for a therapeutic decision. Thus, there is a decisive moment in the clinic when there is little room for doubt, and it is easy to see why the processes of EBM – which, to a great extent, consist in managing uncertainty by using evidence of high quality – have not been readily embraced by the surgical pathologist. This initial reluctance is, however, slowly transforming into acceptance: it is hard to claim that pathology is an essential part of the medical practice, but that it is off-limits to the critical analysis driven by the EBM proponents. Practice guidelines have progressively been introduced in the diagnostic work-up of tissue samples, and technological innovation has significantly altered diagnostic methods. New technologies being applied to cytological and tissue specimens demand EBM not only at many points in the course of their development but also in their final application to the analysis of clinical samples.

EBM, a discipline that in part had its beginnings in technology assessment, evolved by adopting methodologies common in other domains of medicine such as epidemiology, but also by learning from the more remote fields of economics, business, and engineering. As it has matured, EBM has been incorporated into medical school curricula, and its principles, constantly refined, are used in the elaboration of widely used practice guidelines and consensus statements.

In this chapter, we consider how the recent advances in science and technology, as well as changes in cultural and social trends, act as powerful forces that argue in favor of the incorporation of the tenets of EBM into the rapidly changing specialty of diagnostic pathology.
discipline of diagnostic pathology. We also consider some of the arguments of those who are critical of integrating EBM in the mainstream of pathology.

The Socio-Economical Context of the Changing Technological Landscape

Since the middle of the twentieth century, the pace of technical evolution in the medical sciences has accelerated. The consequences of this have been wide reaching. The practice of almost every single specialty of medicine today has been drastically affected by the technological innovation resulting from the unprecedented convergence of the progress made in each of several unrelated disciplines. The complexity of practicing medicine increased and required constant adaptation of the healthcare delivery models. Studies undertaken in the 1970s began to show that there was room for improvement in the way medicine was being practiced. Both academics and public interest groups began to question the efficiency of the medical system [1, 2].

Coming hand in hand with the rapid therapeutic and technological advances of the 1960s was a significant increase in the intrinsic cost of treating illness. An increase in diagnostic procedures and means to establish the cause of disease multiplied the cost of health care. Thus from a purely practical standpoint, the need emerged to critically evaluate all new technologies before they would be widely adopted. In 1973, as a consequence of the first oil crisis, the economic burden imposed by the cost of medical care was underscored further as the crisis revealed how vulnerable national economies were to perturbation and how the subsequent destabilization of the economy and inflation affected medicine. Both the cost of health care and the cost of medical research increased. Those bearing the cost of health care, whether governments, nonprofit or private enterprise, began to seek ways to actively manage the resources needed to provide health care. Thus by the last quarter of the twentieth century, it became clear there was a need for a framework through which to look at the objective evidence that was the basis of medical practice.

Finally, through globalization, the industrialized nations realized how much the improvement of the health and life chances of the neediest impacted on the wealthiest. Effective therapies and diagnostic technologies available to the developed nations have not been and are still not yet available to the poor. As a consequence, many of the components of the medico-industrial complex have intensified their engagement in generating robust and cheap diagnostic technologies and therapies suitably adapted to be deployed in the developing world and among underserved populations. As these new tools are created and used in the clinic, each requires a rigorous evidence-based analysis of its precision and efficacy.

Recent Forces Reshaping the Practice of Pathology

At the core of EBM is the question of how we handle information that serves to support medical intervention. What value we decide to place on the information, how we go about obtaining new information, and how we compile existing knowledge are all crucial processes of EBM. And of paramount importance is how we obtain the information pertinent to the diagnosis and management of a single patient.

In recent years, pathology, and more specifically diagnostic pathology, has undergone profound change due to the rapid accumulation of basic knowledge and due to the rapid, almost vertiginous, development of technologies that expand the possibilities of tissue and cell analysis. New information, which is not necessarily clinically worthwhile, is accumulating so fast that it is difficult to distinguish the truly important content from the noise. This proliferation of available information is another reason why the principles of evaluating the value of the evidence are becoming ever more crucial for both the general practitioner and the academician.

In laboratory medicine, two types of information are used in medical decision-making: (1) laboratory values and (2) anatomical pathology
diagnoses and values. Each of these two subdisciplines has its specific challenges and is moving toward EBM at a different speed. Because of its interpretative nature, however, anatomical pathology tends to remain anchored in “eminence-based medicine” mode rather than relying on strong grades of evidence. It is precisely here, in the realm of tissue analysis, that modern technologies are opening inroads and calling for the rigorous use of evidence-based tools. The tissue samples interrogated under the microscope are now amenable to a workup that provides resolutive answers to the questions raised by the diagnostic pathologist. The question is not only what kind of disease, process, or lesion are we confronting but also what is the best and most efficient therapy and what response is to be anticipated.

The first tissue analysis technology to make an impact in diagnostic surgical pathology was immunohistochemistry (IHC), and it has served as an effective vehicle for the adoption of EBM. For example, IHC not only provided evidence for a diagnosis but it also began to introduce quantitative histopathology by enumerating cells expressing a given antigenic determinant. Where the quantitative approaches of morphometry had failed to impact daily diagnostic practice, IHC changed it by storm and brought the rigor of the laboratorian to histopathology, creating best practices, practice algorithms, and practice standards [3].

Yet one of the most profound developments to affect the practice of medicine in the last 20 years has unquestionably been the emergence of the field of molecular medicine. Molecular medicine has brought unprecedented knowledge about the pathogenesis of many diseases and served as a rational basis for therapy design. Molecular technologies have brought and continue to bring constant innovation to all branches of laboratory medicine, and with that, a quantum leap in the volume of information to be managed. The ability to extract tissue components such as proteins or nucleic acids from tissues and subject them to a comprehensive analysis has provided us with high-density data sets (“omics”) that can be mined by artificial intelligence [4]. The general strategy is to reduce these large assemblies of data to a few features that can then be turned into a clinically applicable test in the laboratory. In other instances, PCR-based approaches applied to a micro-dissected sample enable the pathologist to detect with specificity an infectious agent or a genetic lesion and thus diagnose with precision the etiology of a lesion.

The modern tools of molecular diagnostics allow us to obtain information from a patient with unprecedented precision and breadth. Two tumors arising in the same organ and histologically similar can now be sorted out by analyzing which signal transduction pathway is preferentially and differentially activated in each one of them or what specific mutational spectrum is present in each one of the tumors [5–7]. The molecular alterations found in each tumor may dictate specific targeted therapies. This type of characterization of a lesion is the basis for personalized medicine, “the right treatment for the right person at the right time,” and the cornerstone for predictive medicine: the ability to predict the response of an individual patient to a specific therapy. The crucial characteristics of this type of evidence are (1) its objective precision inherent in modern molecular analytical techniques and (2) the fact that in most instances the molecular alteration is causally linked to the pathophysiology of the disease. When present, the causal nature of the link established by experimental studies and refined by observational and therapeutic studies in the human constitutes the highest quality of evidence upon which to base a targeted therapy for an individual patient.

With the availability of reliable, fast, and economic sequencing technologies, the individual genome is becoming a reality, and it has been argued that the requirements for the recovery of clinically useful insights from an individual’s genome are different from those of traditional cohort-based medical knowledge.

Since evidence rules must be applied to the singularity of the individual (her or his unique sequence), we ought to consider how the traditional tenets of EBM will be applied to specific information only valid for a single patient. The case is being made for an alternative approach
Based on translational engineering and intelligence (biointelligence) for interpreting the genomic information from an individual patient [8]. The ability to sequence the 1–2% of a patient’s genome that encodes for structural proteins of the cell can enable the detection of disease causing mutations in a single patient. For example, the detailed examination of the DNA of a single patient suffering from Bartter syndrome revealed a novel mutation in the gene coding for a protein responsible for the absorption of water and salt in the intestine. Not only was the case of the index patient resolved, but when other infants with a presumptive diagnosis of Bartter syndrome were examined, five more mutations were identified in the transporter protein [9]. These results illustrate how the new technologies, in this case exon capture and sequencing, generate clinically useful results.

In parallel to the advances in biomedical technologies, there have been advances in information processing, acquisition, and display that have allowed the pathologist to continue as the physician-integrator of information. The capacity of an individual to apprehend and integrate different streams of general evidence and information about a given patient has been progressively taxed. Fortunately, information technology and computational science have come along at the right time, expanding our capacities to display, analyze, and integrate complex and rich streams of data. It is now possible to enlist computational power to carry out the integration of thousands of features and select a small subset of parameters that solve the question (diagnostic, prognostic, predictive). Statistical methods can then be used to test thousands of features for predictive power and select the most powerful ones (feature reduction) to generate a test that can be validated. Modern machine vision technologies that use segmentation, object identification, and topology can derive thousands of objective reproducible features from a tissue section and then proceed to overlay specific molecular markers on the segmented image to produce a “quantitative functional histopathology,” thus creating a powerful and precise diagnostic tool [10, 11].

A task once done by a master diagnostician, who, however, was informed by many fewer elementary features, can now reach every single patient and be performed in a reproducible manner. When done by artificial intelligence as opposed to an unaided human mind, the processing will be repeated without error 100% of the time.

**From Precision Medicine to Efficient Medicine**

With the advent of precision technologies that identify and measure one or several components in a clinical specimen with high specificity and sensitivity or reveal a submolecular alteration, the science of diagnostics enters the realm of “precision medicine.” The evidence obtained is objective and precise, and the principles of EBM can then be turned to the task of refining precision medicine into efficient medicine. Efficiency is to be considered with the patient in mind: Are we subjecting the person to the minimal number of tests necessary to best identify and treat the problem? Are we using the best combination of drugs for that particular patient? EBM offers the optimal path to define the most economical way to deliver the personalized precision medicine that we can provide today. It is important to keep in mind that “economical” is used in the sense of the most benefit for the resources used and not necessarily the cheapest.

In our current climate, the cost of medical resources is a major concern. At a time when the cost of health care is becoming prohibitive for industrialized nations (U.S. health expenditures are projected to reach 20% of the GNP by 2020), the tenets of EBM are being used to base policy and resolve debate. Right-thinking people may come to different conclusions based on the available evidence, but to oppose someone’s evidence-based stance does not require invective, rather facts and logical argument. Many government funding research in healthcare quality are banking on the power of EBM to decrease the rising share of the national economies taken by healthcare expenditures. Costs can be brought down by
Evidence-Based Medicine Must Take the Patient into Account: Participatory Medicine

One of the interesting aspects of the real-world approach in gathering data is taking into account the patient–physician relationship as one crucial component of the system to be analyzed. In fact, we have little detailed evidence of how natural phenomena such as disease interact with a social construct such as a health system [13].

The present emphasis on patient’s choices de facto introduces the patient into the process of generating data. With the information revolution in full gear, much of the knowledge that was exclusive to physicians and other trained health personnel is now accessible to the lay public. Information is read and absorbed with avidity by those facing the distressing but motivating condition of being a patient. Through the aggregation of many patients’ personal experiences, new communities are organized around the commonality of shared medical circumstance, such as physical illness or genetic condition. The formation of virtual communities or support networks, a phenomenon for which Rabinow has proposed the concept of “biosociality” [14], has the potential of becoming an active contributing factor to data sets that can be further mined using computational tools. It does not seem risky to predict that the communication revolution will enable observations made and rigorously recorded by lay individuals to be admitted as “evidence” and form the basis for future observational studies. In the near future, patients will be contributing to shape, in many ways, the evidence with which the EBM methods will generate the “best practice standards.”

Is There Evidence to Support the Need for Evidence-Based Medicine in Pathology?

The overarching argument we have put forth is that the best way to handle the vertiginous changes affecting pathology, particularly diagnostic pathology, is to adhere to the tenets of EBM. Critics of this argument will present a number of objections. They will hasten to point out that there is no robust body of evidence to support our position; that time and resources are limited and are less and less available to busy practitioners; that EBM will require training in additional skills to search for the available information and evaluate the strength of the available evidence; that EBM is “cookbook medicine” and “takes the art out of diagnostic clinical medicine”; that it will threaten current standards of therapeutic excellence as initiatives of the CER type use EBM to cut costs without regard for the quality of care [15].

It is certainly true that stricto sensu there is no formal evidence to support EBM. A randomization study of traditional style versus EBM practice style in diagnostic pathology is practically impossible and would very likely be unethical. The fact is, however, that pathologists, because of
the nature of their practice, have operated close to EBM standards for a long time and have more often than not recorded their diagnostic outcomes in observational studies involving case series or, more recently, in studies coupled to clinical trials. The leap to formalizing the principles of EBM in the practice of pathology is not great. As a discipline, pathology has traditionally been seen as providing “the evidence,” and yet pathologists and clinicians have come to realize that appearances can be deceiving and that very similar if not identical morphologies can have very different clinical behaviors that demand different therapeutic strategies. Not knowing how to distinguish the mimics from the authentic lesion constitutes individual ignorance that can be repaired by acquiring the knowledge to make the distinction. By contrast, being confronted by lesions that are identical and thus indistinguishable but with a very different behavior constitutes collective ignorance. Two prominent examples presenting a dilemma rooted in this type of ignorance are intraductal low-grade breast cancers and prostate cancers with a Gleason grade of 6 or less. Both are early cancers often found in asymptomatic patients at screening, and their therapy ranges from watch-and-wait surveillance to aggressive intervention designed to eradicate the tumor. We are just beginning to learn how to make such distinctions, making appeal to objective tools such as the ones used in systems pathology. Conclusive evidence upon which to base a distinction and rational therapy will hopefully be validated in the near future.

The paradox is that the same diagnosticians who have acquired new powerful tools must now seek additional evidence to support their reasons for saying what they say, for diagnosing what they diagnose, and for recommending what they recommend. In other words, pathologists have transitioned from embodying the evidence to having the tools to uncover it and having to justify the use of these tools. The principles of EBM may not be perfect, but they are probably the best for the evaluation of technologies, codifying their use in practice, and assessing their cost and effectiveness. The accuracy, value, and efficacy of these new ways must be methodically documented, ideally by randomized trials that compare a new diagnostic or predictive modality to the conventional approach used to solve a specific clinical problem. It behooves the practitioner working on a specific case to follow the well-defined steps involved in the practice of EBM: (1) convert information needs into answerable questions, (2) track down the best evidence with which to answer these questions, (3) critically appraise the evidence for its validity and importance, (4) integrate this appraisal with clinical expertise and patient values to apply the result in clinical practice, (5) evaluate performance. Adherence to these tenets will go a long way to manage uncertainty in clinical practice.

Objections to EBM, on the basis of the increasingly limited time and resources available to busy practitioners and on the perceived additional burden of developing the skills necessary to search for the available information and evaluate the strength of the available evidence, raise legitimate concerns. Fortunately, however, the IT revolution has gone a long way to mitigate these factors. The skills necessary to access information can be learned at any stage of clinical training and are now taught to medical students in most medical schools. More articles of the “systematic review” type are appearing in general, not just in subspecialty journals, and brief summaries of evidence relevant to common clinical questions can be accessed at the point of care.

Many of the objections articulated by opponents of EBM are based more on misperception than on substance. Two of the major arguments of opponents to EBM are that “it is cookbook medicine” and that “it takes the art out of clinical medicine.” Following the principles of EBM does by no means exclude creativity. The best clinicians are the ones capable of making cognitive connections between facts and rules. That is the product of a creative process—a process that, if grounded on the rules of evidence, will be able to be taught, learned, and constantly perfected.

It is also a misperception that EBM is used by initiatives of the CER type simply to cut costs without regard for therapeutic standards or the quality of care. Those who feel uncomfortable with EBM argue that the use of the findings will not be geared to the benefit of the patient, but to the rationing of health care [12]. As noted earlier, many aspects of EBM lead directly to more effective patient care.
EBM is not designed to answer philosophical questions about the values and priorities of a society and therefore cannot pretend to. But one can strive for a democratically based transparent process that, after informed dialog and debate, will generate a consensus that accommodates the values and priorities of the vast majority of peoples and interests.

**Conclusion**

Modern technologies and ever more incisive methods of tissue analysis are providing increasing accuracy, resolution, and effectiveness to modern diagnostic sciences. We are immersed in a rapidly evolving world where disruptive technologies come at such speed and information is generated in such abundance that EBM becomes an essential philosophical and practical factor of stability. It behooves all of us in pathology to establish EBM as the linkage of technological innovation and research to the resolution of patient illness and problems in the delivery of care.

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