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An observational examination of the literature in diagnostic anatomic pathology

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Original research published in the medical literature confronts the reader with three very basic and closely linked questions—are the authors' conclusions true in the contextual setting in which the work was performed (internally valid); if so, are the conclusions also applicable in other practice settings (externally valid); and, if the conclusions of the study are bona fide, do they represent an important contribution to medical practice or are they true-but-insignificant? Most publications attempt to convince readers that the researchers' conclusions are both internally valid and important, and occasionally papers also directly address external validity. Developing standardized methods to facilitate the prospective determination of research importance would be useful to both journals and their readers, but has proven difficult. In contrast, the evidence-based medicine (EBM) movement has had more success with understanding and codifying factors thought to promote research validity. Of the many variables that can influence research validity, research design is the one that has received the most attention. The present paper reviews the contributions of EBM to understanding research validity, looking for areas where EBM's body of knowledge is applicable to the anatomic pathology (AP) literature. As part of this project, the authors performed a pilot observational analysis of a representative sample of the current pertinent literature on diagnostic tissue pathology. The results of that review showed that most of the latter publications employ one of the four categories of "observational" research design that have been delineated by the EBM movement, and that the most common of these observational designs is a "cross-sectional" comparison. Pathologists do not presently use the "experimental" research designs so admired by advocates of EBM. Slightly >50% of AP observational studies employed statistical evaluations to support their final conclusions. Comparison of the current AP literature with a selected group of papers published in 1977 shows a discernible change over that period that has affected not just technological procedures, but also research design and use of statistics. Although we feel that advocates of EBM deserve credit for bringing attention to the close link between research design and research validity, much of the EBM effort has centered on refining "experimental" methodology, and the complexities of observational research have often been treated in an inappropriately dismissive manner. For advocates of EBM, an observational study is what you are relegated to as a second choice when you are unable to do an experimental study. The latter viewpoint may be true for evaluating new chemotherapeutic agents, but is unacceptable to pathologists, whose research advances are currently completely dependent on well-conducted observational research. Rather than succumb to randomization envy and accept EBM's assertion that observational research is second best, the challenge to AP is to develop and adhere to standards for observational research that will allow our patients to benefit from the full potential of this time tested approach to developing valid insights into disease.

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"*Put genius in possession of a wrong method for learning of the world, and genius will fly ever more quickly to error and fancy.*"
Francis Bacon, 17th Century Philosopher [Cited by Dr. Alan Kors, Professor of History, University of Pennsylvania].[1]

"*There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling and too unjustified, and no grammar and syntax too offensive for a paper to end up in print.*"
Dr. Drummond Rennie, former Deputy Editor of the New England Journal of Medicine and JAMA [and self-described as "cranky"].[2]

At heart, anatomic pathologists are sophisticated taxonomists whose diagnostic decisions are founded on important insights that were achieved by their predecessors from observational studies that often lacked controls and seldom employed statistical analysis. However, roughly 25 years ago, a movement began in pathology to supplement traditional morphologic data with information regarding cellular proteins and nucleic acids. As a result of that trend, a significant portion of current anatomic pathology (AP) research either evaluates or utilizes techniques that provide objective data unavailable to prior generations. This technical revolution begs the question as to the nature of AP research in the 21st century. Will new technologies simply be grafted onto the case- series and case-report studies of the 19th and 20th centuries, or will the rapidly increasing sophistication of the diagnostic database and its statistical analysis be accompanied by improvements in research designs? Review of the publications in some clinical journals documents that in association with an increase in sophistication of technical methodology, the research has been transformed by improvements in study design. As a result, journal editors and readers evaluate the "believability" of any given paper—at least in part—by judging the credibility of the research design chosen by the authors. Various hierarchical rankings of research design generally show a commonality of their essential features[3,4] (Table 1).

Any discussion of the medical research literature must acknowledge that it represents a highly diverse collection of communications which vary from original research to subject reviews, obituaries, book reviews, and presidential addresses. Even in the category of original research papers, there is likely to be marked variation in the nature of paper's goals and conclusions. One publication may aim to increase the understanding of particular tissue abnormalities, whereas another might consider the utility of standardized reporting forms, and a third may attempt to assess diagnostic precision. Obviously, such an aggregation cannot be held to any one standard for the continuous variable of "importance." In contrast, it is not unreasonable to expect published research to be valid.

Table 1 Evidence hierarchy

Evidence from well-designed randomized controlled trials.
Evidence from well-designed experimental trials without chance randomization.
Evidence from well-designed cohort or case-control observational studies.
Evidence from well-designed cross sectional studies.
Opinions of respected authorities, including reports of expert committees.
Evidence from descriptive studies.

Distinguishing between validity and importance

Validity and importance are related but very different characteristics of medical research. Conclusions can be incontrovertible but have no practical significance. In contrast, they may be invalid but still important if pathologists rely on the research to make diagnoses that influence clinical management. Furthermore, although the validity or importance of a published paper can sometimes be apparent at a glance, more often these characteristics are difficult to assess. Prospective evaluation of research importance has been particularly difficult to standardize, and it remains largely an "I-know-it-when-I-see-it" phenomenon that commonly requires the benefit of hindsight. For example, one popular method of retrospective evaluation of importance is counting the number of times that a published paper is cited by other authors.

In contrast to importance, the *prospective* evaluation of validity in medical research has been placed on a more scientific footing by the Evidence-Based Medicine (EBM) movement. One of EBM's principles holds that there are several different viable types of investigational design, and differences between these designs may well impact the validity of final conclusions. Advocates of EBM contend that data quality and data analysis meld with research design to provide a foundation for judging research validity. When publications provide transparent descriptions of all three elements, reviewers and readers are able to evaluate the validity of the study in question.[5]

Is there a common pathway to validity in medical research?

In contrast to the obsessive attention to research design evident in medical literature that has been most influenced

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