THE TOTALITY OF EVIDENCE

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FRONT LINE COVID-19 CRITICAL CARE ALLIANCE
PREVENTION & TREATMENT PROTOCOLS FOR COVID-19

WHAT IS EVIDENCE-BASED MEDICINE?

Decision making in medicine can be difficult.

Evidence-based medicine is a systematic approach to medicine in which doctors and other health care professionals use the **best available scientific evidence** from clinical research to help make decisions about the care of individual patients.

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GOOD DECISIONS ARE BASED ON:

- the best available evidence;
- the clinician's experience, knowledge, and skills;
- the patient's individual circumstances, wants, and needs.

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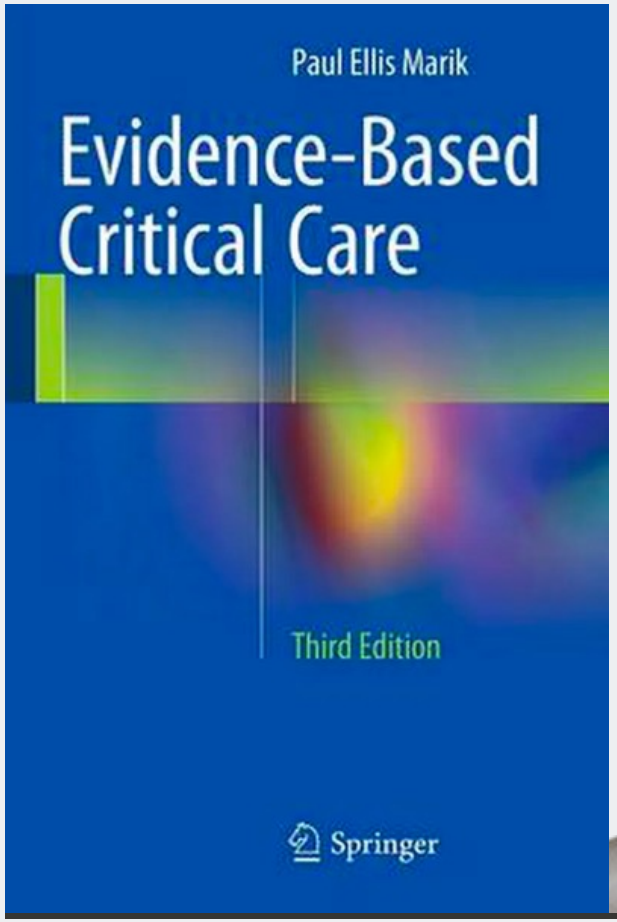
DID YOU KNOW?



I wrote the premier textbook on Evidence-Based Medicine in Critical Care? (not to brag or anything...)

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EVIDENCE COMES IN MANY FORMS

- systematic reviews and meta-analyses (SRMAs)
- randomized controlled trials (RCTs)
- observational controlled trials (OCTs)
- epidemiological analyses
- case series
- patient anecdotes

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THE TROUBLE WITH SRMAs

Can lead to inaccurate results because of

- biased inclusion or exclusion of study data
- flawed analyses
- the exclusion of unpublished studies

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THE TROUBLE WITH RCTs

- heavy influence of the pharmaceutical industry in the design and execution of studies
  - particularly in the larger, well-funded studies published in high-impact medical journals
- Studies can be, and often are, designed to produce a particular set of results
- Often RCTs do not accurately reflect real-world clinical impacts because of their biases and flaws

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THE UNDUE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY ON CLINICAL RESEARCH

Many doctors, researchers and medical ethicists have been issuing warnings for years, including editors of some of the world's major high-impact journals

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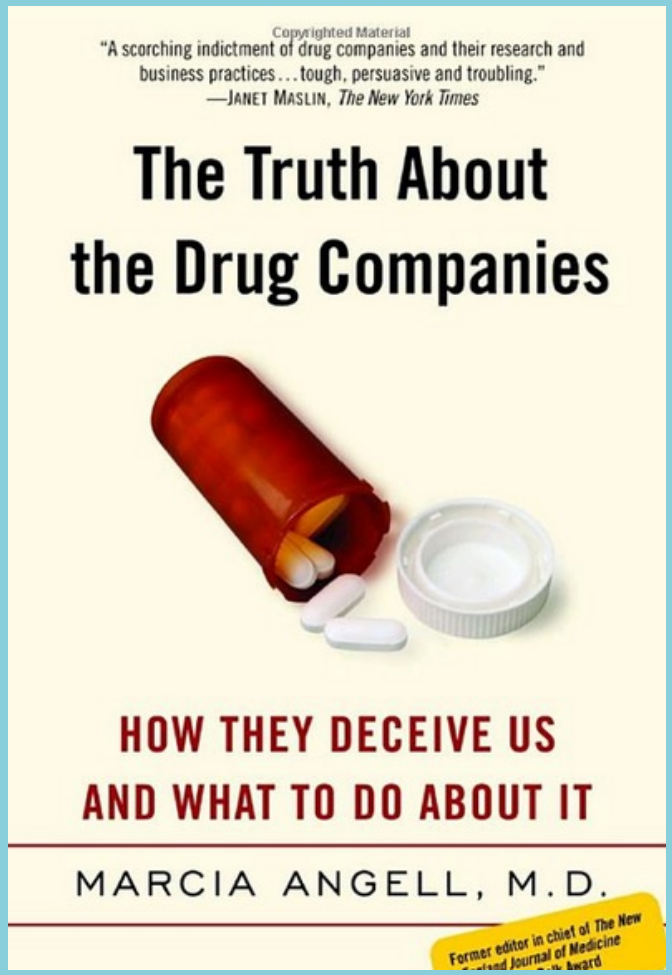
It is **simply no longer possible to believe** much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. **I take no pleasure in this conclusion**, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine.

Marcia Angell
Former Editor-in-Chief
New England Journal of Medicine



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The case against science is straightforward: much of the scientific literature, perhaps half, may simply be untrue... In their quest for telling a compelling story, scientists too often sculpt data to fit their preferred theory of the world. Or they retrofit hypotheses to fit their data.

Richard Horton
Editor-in-Chief
The Lancet

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... for most study designs and settings, it is more likely for a research claim to be false than true.

Moreover, claimed research findings may often be simply a measure of the prevailing bias.

John P. Ioannidis
Professor of Medicine
Stanford University

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

Published research findings are sometimes refuted by subsequent evidence, with ensuing confusion and disappointment. Refutation and controversy is seen across the range of research designs, from clinical trials and traditional epidemiological studies [1–3] to the most modern molecular research [4,5]. There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims [6–8]. However, this should not be surprising. It can be proven that most claimed research findings are false. Here I will examine the key factors that influence this problem and some corollaries thereof.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p-value less than 0.05. Research is not most appropriately represented and summarized by p-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

should be interpreted based only on p-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful. "Negative" is actually a misnomer, and the misinterpretation is widespread. However, here we will target relationships that investigators claim exist, rather than null findings.

As has been shown previously, the probability that a research finding is indeed true depends on the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance [10,11]. Consider a 2×2 table in which research findings are compared against the gold standard of true relationships in a scientific field. In a research field both true and false hypotheses can be made about the presence of relationships. Let R be the ratio of the number of "true relationships" to "no relationships" among those tested in the field. R is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2×2 table, one gets $PPV = (1 - \beta)R/(R - \beta R + \alpha)$. A research finding is thus

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Abbreviation: PPV, positive predictive value

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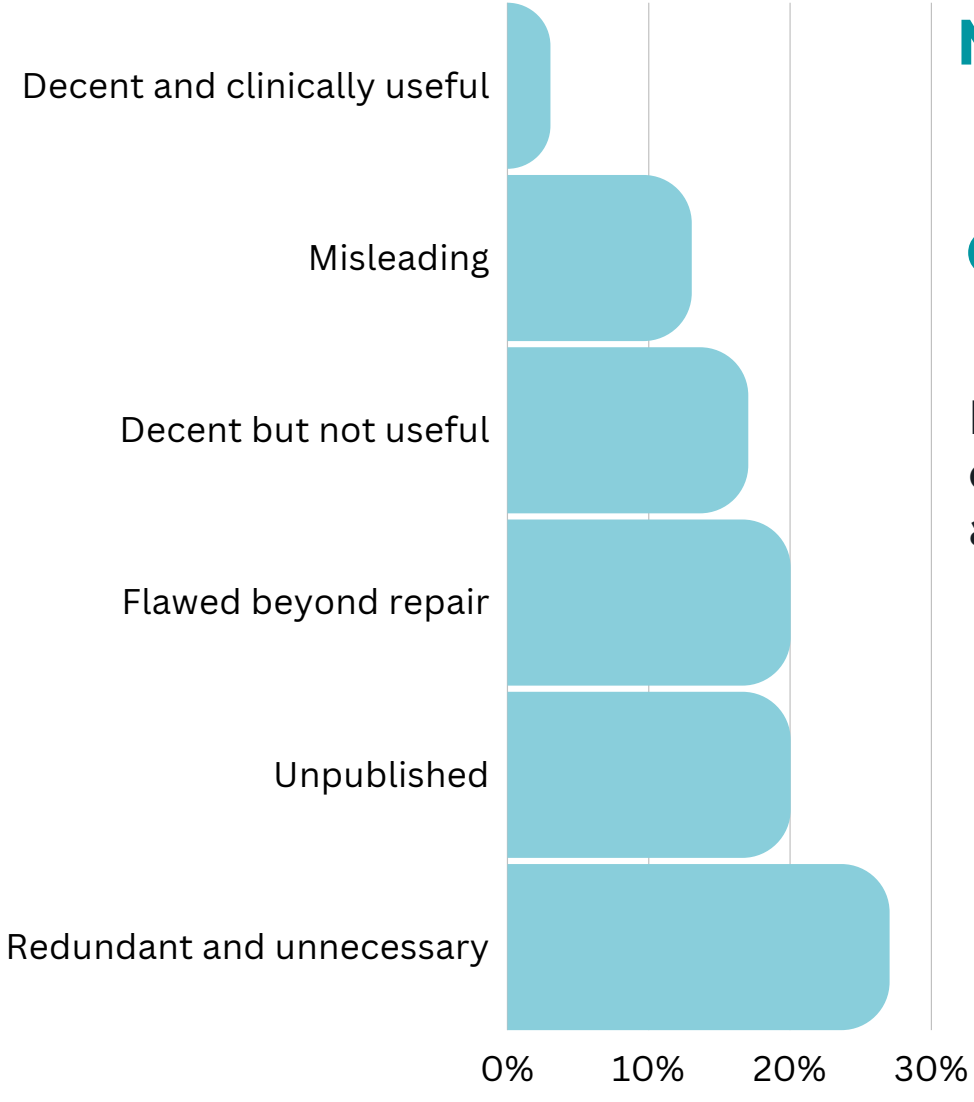

MASS PRODUCTION OF REDUNDANT, MISLEADING AND CONFLICTED CLINICAL RESEARCH

In 2014, Prof. Ioannidis analyzed over 9,000 published meta-analyses

- **1 in 5 were flawed beyond repair**
- **1 in 3 were redundant and unnecessary**
- **Some were decent but had "noninformative" evidence**
- **Good and truly informative meta-analyses were a small minority**

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A NEW MODEL: WEIGHING UP ALL THE EVIDENCE

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THE TOTALITY OF EVIDENCE APPROACH

We propose that researchers rely on the 'totality of evidence' and incorporate data from

- basic science
- pharmacology
- epidemiology
- clinical experience
- OCTs, RCTs, and SRMAs

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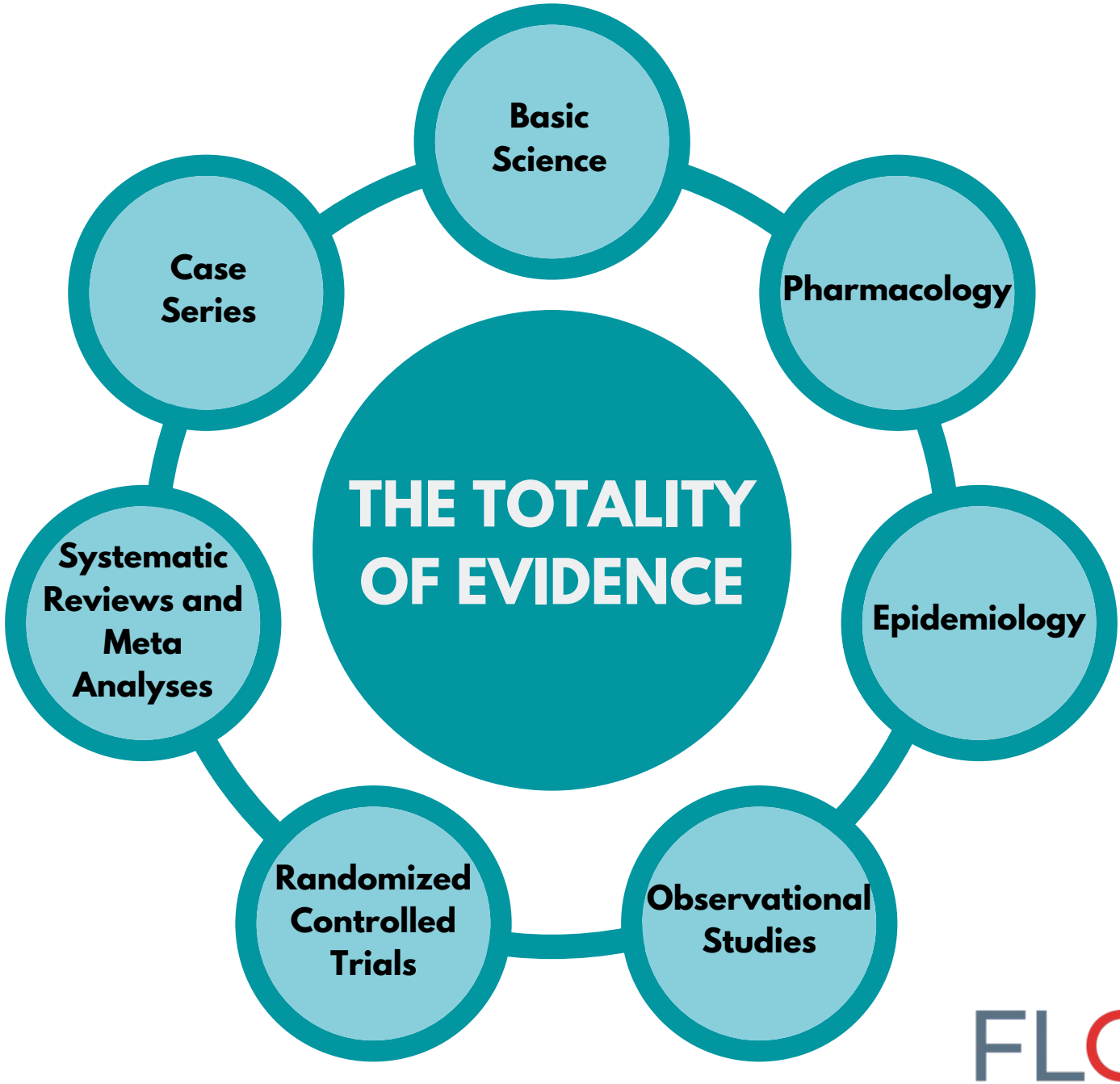

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