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CQ REVIEW

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The main goal of the Book Review Section of Cambridge Quarterly is to cultivate a place where scholars can share their thoughts on broad philosophical topics sparked by noteworthy books. Instead of focusing narrowly on works in healthcare ethics, our reviews cast a wider net, so that we may reflect on diverse ideas. Please email dien.ho@mcphs.edu, if you have book recommendations or if you are interested in writing a review.

Malignant: How Bad Policy and Bad Evidence Harm People with Cancer, by Vinay Prasad, Baltimore, Maryland, Johns Hopkins University Press, 2020.

In 2018, my father's cousin Paul called to tell me that he was diagnosed with a subcutaneous melanoma. Paul was charismatic and smart, he had had an adventurous life, working for the Foreign Service and the United Nations, first in London, and then spending 20 years in Haiti. He was a devout environmentalist, and fought passionately for the creation of a national park in Haiti. What I most cherished in Paul personally, however, was that he always encouraged me to speak out about what mattered to me—even when what I was saying was controversial, or likely to be unpopular. Paul's cancer was stage IV—this meant that his time was short. What was devastating for me, however, was witnessing his struggle over the next year and a half. Despite the fact that he was not initially identified as a good candidate, he fought to enter into a clinical trial for a new cancer drug after first line therapies failed. He was convinced that this drug would save him. Although the new drug did help him at first, allowing him to return to activities he loved, his last months were especially difficult, and he ultimately died from toxic side effects. He pinned so much hope on this new therapy, but like many new cancer drugs, this drug too did not live up to the hype. Paul's story is—sadly—not uncommon, and Prasad's book explains why.

Vinayak Prasad's new book, *Malignant: How Bad Policy and Bad Evidence Harm People with Cancer* is courageous and devastating. All future clinical oncologists should read this book, as should everyone involved in testing and regulation of approval of new cancer drugs, and last but not least: cancer patients, and their families, especially those patients considering whether to participate in a clinical trial. Prasad documents why many new cancer treatments are not living up to their often overhyped promise. There are several reasons: surrogate endpoints fail to predict which drugs improve overall survival; accelerated approval is granted for drugs that do not meet the criterion of serving an "unmet" need; United States Food and Drug Administration (FDA) approval is granted for drugs that are substandard—either because tested against poor comparators, or approved for minimal improvements in surrogate outcomes; historical (uncontrolled) trials overestimate benefit; arguments from biological plausibility are often oversold; enthusiasts hype drugs before demonstrated to be effective; and there is a revolving door between the FDA and the very same pharmaceutical companies that seek approval for new drugs. The book can be difficult to read (perhaps especially so for both advocates for new therapies and patients who want to believe the hype), but I hope very much that this book gets a wide audience, and that people pay attention. Prasad is sticking his neck out; if he is correct, we desperately need to rethink the policies governing the testing and promotion of new cancer treatments.

Prasad explains in plain, clear terms, how different kinds of cancer trials work; though more often, he shows how they fail to work, or can be manipulated to yield desired results. He shows in careful detail

how "upstream" questions in clinical research—about trial design, choice of endpoint, or selection of patient participants—can shape which drugs get approved, for better (and unfortunately, far more often, for worse, at least, for patients). He demonstrates in excruciating detail how the process of drug testing and approval, the hype and hope around new drugs, has real impact on patients' lives. The book does an excellent job of defining and explaining otherwise complex issues in a way that anyone could understand. Indeed, those of us who teach philosophy of medicine or biomedical ethics could use this book as a tool for teaching how to critically appraise clinical research. The book demonstrates how what may seem to be "purely scientific" questions about what we measure, and how, involve value-laden choices.

As I typed the above sentence, I could feel many scientists bristling. The suggestion that even "good" science is not value free can seem like a threat to scientific objectivity. However, this book provides a valuable lesson in how even "good" scientists cannot dodge very difficult value-laden questions. Unfortunately, some such choices become routinized, such that clinicians or clinical researchers may not be thinking as carefully as they should about whether, and how well, what we are measuring is relevant to what we ultimately care about. In addition, he explains how regulatory standards set out to protect patients are not enforced as they should be—which is, frankly, shameful. For example, despite the fact that for drugs receiving accelerated approval, the FDA requires follow-up "phase 4" trials to determine whether surrogates do predict clinical endpoints, such studies are often simply not conducted.

Prasad opens the book with the case of autologous stem cell transplants—a case of overselling an ineffective therapy, with huge financial costs, not to mention costs to human life. By the end of the book —given the scope of the problems he documents, from inadequate regulation, to financial conflicts of interest, to the vast array of suspect research designs—this case seemed relatively mild. Indeed, one might excuse this earlier case as a kind of group think or bandwagon effect, founded on oversold plausibility of a mechanistic hypothesis. By contrast, the extent of currently overhyped cancer therapies was—frankly—overwhelming, and at moments, unbelievable. I could not help wondering whether the current state of affairs was as bad as he claimed. For, the extent of manipulation, overhyped promises, and rampant use of misleading data, models, and cost–benefit estimates, was truly horrifying. I kept wondering whether it was really possible that such harmful practices have continued unabated.

Yet, Prasad has been documenting these patterns for decades. Although I cannot possibly summarize the key upshots of the book in the depth they deserve, here are some of the key insights he (and others he cites throughout) have been documenting over the past 15 years:

> Costs of cancer drugs far outstrip the cost of production (including upstream research), to the extent that the profit margin on cancer drugs is higher than almost any other industry. Moreover, there is no correlation between cost and effectiveness; drugs that merely extend life 2 months, versus 20 months, are not proportionately less expensive.[1]

- Surrogate endpoints (e.g., response rates and progression free survival), in testing new therapies for cancer are on the rise, in part due to accelerated approval of many drugs, which in principle should be followed by demonstration that such surrogates do track clinically relevant outcomes like overall survival.[2]
- Many such surrogates are poor predictors of clinically relevant outcomes,[3,4] and in almost 50% of cases, follow-up trials are not conducted.[5] That is, drugs are approved and left on the market without any demonstration that the surrogates that they improved actually track clinically relevant outcomes.
- Drugs that receive accelerated approval should in principle do so on the basis of "unmet need." In many cases, this criterion is not met.[6]
- Hype of cancer drugs—overselling the potential benefit, when the benefits have not been established—is widespread.[7]
- Moreover, spin—the misrepresentation of a trial as successful, when the primary endpoint is not in fact met—is likewise common.[8,9]
- Conflicts of interest plague the FDA approval process.[10,11,12]

- The incentive structure for drug testing currently leads to the promotion of drugs tested against weak competitors, sometimes in international contexts where substandard clinical care is provided to controls,[13] and approved for small benefits of dubious clinical relevance.[14]

CQ ReviewPerhaps needless to say, reading this litany of shortfalls can be rather devastating. However, Prasad goes on to offer suggestions for how to reform the FDA approval process, and how to make better progress in cancer medicine, more generally. At least part of this advice is directed at future clinicians and patients, whom he encourages to be more inquisitive advocates for their own interests. The most substantive part of his proposal, however, is a series of straightforward suggestions for revamping of our current status quo for the design of trials and regulation of drug approval. Some are rather simple and could be implemented immediately: refusing to approve drugs tested outside the United States against substandard of care comparators, not approving duplicate drugs for the same purpose unless they show significantly improved survival outcomes in randomized clinical trials, requiring that drugs be tested in patient populations that are representative of the typical U.S. cancer patient (i.e., same age and health status), requiring that drugs receiving accelerated approval actually improve survival or quality of life before they come to the market, and setting the bar higher than a mere average 10-day increase in survival for patients. These seem like no brainers, and could be implemented tomorrow.

More complex, and likely far more controversial, Prasad suggests that "nonconflicted experts decide how and against what to test the drug product." Currently, the process is in the hands of the pharmaceutical industry; the industry designs and pays for drug trials, and hands the final report to the FDA. Prasad suggests instead that the industry bring proposals to an impartial agency, and a collective of "nonconflicted consultants" (e.g., patient representatives, physicians, and methodologists), in consultation with pharmaceutical companies, assesses which trials are warranted, and ensures that drugs are tested against meaningful comparators. A common refrain is that this will slow the pace of science and the time to approval. He flatly contradicts this; suggesting not only that the process could be speeded on but made far more efficient—not in terms of number of drugs approved, but number of effective drugs approved, making best use of patient participants in clinical trials. Although he has amply demonstrated here the lack of efficiency and cost to patients and insurers (in terms of approval of relatively ineffective and costly drugs) of our current system, I leave to the lawyers and economists whether his optimism regarding this less profit-driven alternative regulatory system is warranted.

Prasad cleverly summarizes his positive proposal for reform of cancer policy using the "hallmarks" of cancer infographic—made famous by Douglas Hanahan and Robert Weinberg's "hallmarks of cancer" paper.[15] It comes down to some basic principles: "independence—entities must be free to advocate for their constituencies; evidence—measure what matters, and do it fairly; relevance—our studies must aid average people with cancer; affordability—successful therapies must be broadly affordable; and, possibility—the preclinical pipeline must be expanded." In sum, researchers should be impartial, and not subject to the influence of economic interests, evidence should be high quality—ideally, randomized against the standard of care—in "relevant" populations (the average person with cancer, not healthy, young patients for whom benefits will be more likely to be discovered), successful therapies should be affordable, and research should be broadened to include novel basic science research; last but not least, we must not waste the time and lives of research subjects generous enough to devote their lives to science by doing redundant studies on "me-too" drugs, that show little promise and less benefit to future patients.

Prasad is a consummate gadfly; he asks at each point of the cancer drug pipeline: Are we doing this as well as we could? Is this the best evidence possible for the best outcome for patients? Whom does this process benefit? What Prasad asks of us is that we step back, look at the big picture, and pause to ask: What constitutes a genuine improvement in outcome? What side effects are "tolerable"? How much and what kinds of evidence are good—or good enough—to warrant approval of new therapies? These are difficult questions with huge import for the future of cancer care. Indeed, how we answer these questions will have implications for the U.S. health care system and economy more generally; for, cancer drugs and profits from them shore up many less profitable elements of our health care system. Their answers thus should not

be left to those with the greatest interest in promoting new drugs. If Prasad is correct about the current policies and standards for testing, leaving such matters to interested parties has led to serious harms. We can and should do far better.

Notes

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