Malignant by Vinay Prasad:
Oncology's Leading Gadfly

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Self-described sceptic, hailed by some as 'iconoclast-in-chief,' by others as a staunch patient advocate and 'evidence-based' crusader, the vociferous hematologist-oncologist and meta-researcher Vinay Prasad has earned himself a reputation amongst clinicians, researchers and health policy analysts through his provocative academic articles, popular podcast, and—not least—expansive Twitter presence. His work has also not gone unnoticed by philosophers of medicine, a field long engaged with problems that preoccupy Prasad, from issues of medical evidence and clinical trial methodology to genomics and precision medicine.

Prasad now adds a second book to his impressive publications, *Malignant: How Bad Policy and Bad Evidence Harm People with Cancer* (2020), released just one year after his first, *Ending Medical Reversal: Improving Outcomes, Saving Lives*, which he co-authored with Adam Cifu (2019). *Malignant* coalesces Prasad's research into a sustained argument and a call for change in cancer research and policy, tackling a range of problems from clinical trial design and lax drug-approval mechanisms to misaligned pharmaceutical incentives and financial conflicts of interest. Some of this material will no doubt be familiar to Prasad's sizeable Twitter following, where many of his views have been aired in pithy 140-character bursts. Though these appear in edited form in *Malignant* (with expletives omitted), Prasad does not shy away from controversy, and lays out his argument in lucid, readable prose.

At the outset of *Malignant*, Prasad states his thesis with characteristic clarity: "This is a book about how the actions of human beings—our policies, our standards of evidence and our drug regulation—incentivize the pursuit of marginal or unproven therapies at lofty and unsustainable prices" (2020, 1). The remainder of the book is spent supporting this argument. Part one discusses cancer drugs, and he demonstrates how pharmaceutical prices are not determined by clinical benefit, nor are they justified by research and development costs (a considerable amount being subsidized by public funding), but rather based on maximum profit that can be extracted from patients and insurers. He cites the example of chimeric antigen receptor T-cell (CAR-T) therapy, a recent darling of cancer therapeutics, which has found widespread application in hematology-oncology and is moving to earlier

lines of treatment for several diseases. Despite its promise, CAR-T therapy comes with a hefty price tag—as high as US$475,000 for one product, well above the estimated manufacturing costs of US$20,000, which does not include the associated costs of administering, monitoring and treating common toxicities. Prasad points out the elephant in the room in oncology, and a looming question for health systems worldwide: how will we afford the exorbitant and rising costs of new cancer therapies?

In addition to unsustainable costs, Prasad further argues that many new drugs gain approval despite marginal—and often dubious—clinical benefits. He devotes a chapter to discussing oncology's reliance on surrogate outcomes, highlighting how commonly used measures such as response rate (RR) and progression-free survival (PFS) are often arbitrarily defined and lack validity, correlating poorly with clinically meaningful outcomes such as overall survival (OS) or quality of life. Despite this, surrogate outcomes increasingly form the basis for the United States Food and Drug Administration (FDA) approval of new cancer drugs, used in 66 per cent of approvals between 2009 and 2014 (Kim and Prasad 2016). Moreover, in most cases there was a lack of evidence correlating the surrogate with OS, and the majority of approved drugs had no post-marketing demonstration of OS or other patient-centred benefit (Chen, Haslam and Prasad 2020).

Granted, Prasad does not oppose the use of surrogate outcomes altogether; rather, he makes the reasonable argument for the use of well-validated surrogates for drug approval in select cases, which should be followed by robust post-marketing efficacy assessment. Indeed, selecting the most appropriate outcome measures carries several epistemic and ethical considerations. For example, while evidence of OS benefit may be desirable, its demonstration may come at a cost of larger and longer clinical trials, potentially incurring unnecessary harms where a well-validated surrogate may be sufficient. For diseases such as multiple myeloma, where OS for many patients can approach a decade, trials often rely on surrogate outcomes such as PFS, which has previously been validated as a predictor of OS (Cartier et al. 2015). Despite this correlation, however, there are trials in myeloma where PFS and OS have diverged; for example, when a novel drug such as venetoclax may be effective at delaying progression but come with a cost of toxicity and treatment-related mortality (Kumar et al. 2020). While correlating a surrogate such as PFS with OS may be necessary for its use, it is not sufficient in all cases. Biomarkers, such as minimal residual disease (MRD), are the next wave of surrogate measures in hematology-oncology and are increasingly being used in trials as validated predictors of survival (Munshi et al. 2017). The epistemic status of biomarkers has been debated in philosophical circles (see, for example, Hey 2015; Plutynski 2020); whether biomarkers such as MRD negativity can overcome the limitations of cruder surrogates such as RR, or simply represent a reductionism further abstracted from clinically significant endpoints remains to be seen. While many of these questions can be addressed empirically, the context dependence of surrogates and biomarkers underscores the need for more critical, granular analysis of trial outcomes to inform drug approval. Prasad's overview of FDA approval data from the United States highlights how, in many cases, sound analysis is jettisoned to expedite drug approval, with industry-sponsored trials targeting poorly validated surrogate outcomes as a means of providing fast 'evidence', which often lacks meaningful clinical import.

How did oncology arrive at this state of affairs? Part two of Prasad's book engages with the 'societal forces that distort cancer medicine,' tackling issues of 'hype' surrounding novel therapeutics and financial conflicts of interest. He offers an indictment of the loose language employed in oncology—from indiscriminate labelling of disease areas as 'unmet needs' in order to accelerate drug approvals to widespread use of superlatives such as 'game changer,' 'breakthrough,' 'miracle' and 'cure,' which serve to inflate claims of efficacy. He paints a

grim picture of a field where marketing slogans have replaced sober discussion in many forums. As Prasad points out, rhetoric matters, citing a 2014 trial, which demonstrated how rewriting abstracts with positive 'spin' improved oncologists' perception of benefit, despite identical data (Boutron et al. 2014). Prasad's discussion of financial conflicts of interest will be familiar to many readers but his meta-research programme adds substantial and particularly troubling data from the field of oncology. He targets academic medicine, showing how oncology's 'thought leaders'—from guideline authors to national conference speakers and editorialists of major journals—are often heavily conflicted (Mitchell, Basch and Dusetzina 2016) and far from being a hindrance, financial payments from the biopharmaceutical industry are positively associated with academic output (Kaestner, Edmiston and Prasad 2018).

Prasad even takes on Twitter, his preferred medium and an increasingly popular forum for academic exchange, showing how the majority of hematologists and oncologists on the platform have financial conflicts of interest with no disclosure requirements (Tao et al. 2017). But Prasad does not stop at physicians, reviewing how many so-called patient advocacy groups, which remain conspicuously silent on issues such as rising drug costs, draw significant funding from the biopharmaceutical industry (Abola and Prasad 2016). Lastly, Prasad confronts regulators, focusing on the Oncology Drug Advisory Committee at the FDA, the most influential body for determining cancer drug approval in the United States. He reveals how many reviewers go on to hold positions as industry employees and consultants, suggesting a 'revolving door' between regulatory agencies and the biopharmaceutical industry (Bien and Prasad 2016) and raising concerns of regulatory capture of the FDA's drug approval processes.

This part of Prasad's book offers some common-sense solutions, such as ending pharmaceutical funding of oncology conferences and patient advocacy organizations and mandating that FDA employees relinquish industry ties. Prasad's aim is 'independence'—to draw a clear line between processes of pharmaceutical development and marketing, on the one hand, and the methods of clinical research and mechanisms of drug approval, on the other. While Prasad's recommendations are important and necessary first steps, one wonders how effective they will be without addressing the fundamental structures of biomedical research, which in capitalist societies have become inextricably linked to private interests, exemplified by the growth of industry partnerships at most major research universities and hospitals, shaping the entire direction of the field, from diagnostics and drug development to clinical trials. Most philosophers will view attempts to demarcate the 'science' of cancer medicine from 'societal forces' as self-defeating; nonetheless, one can get behind Prasad to pick the low-hanging fruit, where particularly nefarious conflicts confound ethical practice.

On the topic of hype, Prasad devotes a chapter to precision medicine, another area previously examined by philosophers of medicine (Plutynski 2020; Tonelli 2018; Lemoine 2017). He points out how precision medicine's vague and shifting definitions create confusion and hinder critical evaluation. This is unsurprising given personalized and precision medicine's initial emergence as pharmaceutical branding effort rather than an operational research programme, a topic explored by James Tabery (2020) and discussed in detail in his forthcoming book. Prasad sees precision medicine as a seductive hypothesis, but also recognizes that it is supported more by hype and anecdote than by evidence. He highlights problems of validity and reproducibility of genetic testing, as well as issues with evaluating targeted therapies in clinical trials. The chapter provides an overview of some key epistemic challenges in precision medicine in need of further exploration. Prasad recommends his preferred method, the randomized controlled trial (RCT), as a means of

clarifying precision medicine's role, proposing to randomize patients with relapsed cancer to therapies based on genetic sequencing data versus histopathology. While such a study may be insightful for a particular cancer where subsets of patients harbour testable 'driver mutations' and where corresponding targeted drugs exists, one would hesitate to draw more general conclusions about the role of targeted therapy in all of oncology from such a trial. The complexity of cancer genetics introduces a host of challenges, from defining driver mutations to accounting for genomic context that can modify the significance of a particular mutation (Papaemmanuil et al. 2016), not to mention the difficulties of developing clinically validated assays and well-tolerated targeted therapies. While an RCT may be useful to guide clinical decision-making in specific scenarios, any single trial is prone to underdetermine the complex causal networks at play (Chin-Yee 2014). Prasad would likely agree that it is best to abandon attempts to validate or discredit terms such as 'precision medicine' *tout court* and rather get on with good science.

Part three of *Malignant* delves deeper into problems with clinical trial design and also discusses global oncology, examining ethical issues conducting trials in low- and middle-income countries. Prasad reviews arguments against observational studies and historically controlled trials, offering several examples where these approaches have misled in oncology. Unsurprisingly, Prasad settles on RCTs as his preferred methodology for advancing cancer research. Debates over the merits and pitfalls of RCTs are well known to philosophers of medicine and have been ongoing in the field for decades, motivated in large part by the epistemic claims of the evidence-based medicine (EBM) movement (Worrall 2002; Cartwright 2007; Deaton and Cartwright 2018). Like his fellow meta-researcher and intellectual ally John Ioannidis, Prasad shares a zealous commitment to RCTs; likewise, his commitment seems to emerge more from a general scepticism towards observational studies, rather than EBM orthodoxy and its view of RCTs as the 'gold standard' atop an evidence hierarchy (Ioannidis 2018). In this way, Prasad may embody more of the iconoclastic spirit and pragmatic epistemology of early EBM (Goldenberg 2009). Throughout *Malignant* Prasad states his case for favouring RCTs, adding somewhat more nuance than his Twitter persona, who once famously tweeted 'RCT or STFU.' He discusses the methodological advantages of RCTs but justifies his preference for RCTs mainly on inductive grounds, arguing that, in general, RCTs have helped to improve treatment in oncology where prior observational studies or historically controlled trials caused harm. One example was the use of ProMACE-CytaBOM, a particularly toxic therapy used in non-Hodgkin lymphoma based on historically controlled trials but later shown to be inferior in an RCT. Prasad recognizes that RCTs alone are not an infallible cure for oncology's evidence crisis and he emphasizes thoughtful trial design and critical appraisal of findings. He acknowledges, for instance, how problems of multiplicity can still arise with RCTs, where conducting multiple trials of a particular drug can result in positive results by chance alone. To overcome this challenge, Prasad cites a proposal by Jonathan Kimmelman and colleagues who recommend that regulators consider clinical trial 'portfolios' rather than single trials to determine drug approval (Kimmelman, Carlisle and Gören 2017; London and Kimmelman 2019).

Despite his scepticism, Prasad is not a medical nihilist (Stegenga 2018) nor is he pessimistic about the possibility of reforming oncology research and practice for the better. He dedicates part four of *Malignant* to discussing solutions and concludes with chapters offering practical advice to patients and trainees on how to navigate the field and the many challenges faced. Prasad suggests ways to improve processes of drug approval, pharmaceutical reimbursement, and cancer research funding, focusing on three federal agencies in the United States: the FDA, the Centers for Medicare & Medicaid Services and

the National Institutes of Health. He moves beyond his more limited recommendations in part two, proposing broader legislative solutions, including the establishment of an independent federal agency charged with overseeing all aspects of drug evaluation, from clinical trial design to reporting. Again, Prasad's aim is 'independence,' as he argues that 'entities must be free to advocate for their constituencies' (2020, 239); in other words, free to interact in the absence of financial conflicts to arrive at fair policy. Here Prasad seems to cling to a liberal notion of free discussion or 'ideal speech situation,' which may underestimate the social embeddedness of institutions and overestimate the force of rational argument and evidence in policymaking, particularly in the face of powerful political and economic motives to which oncology is certainly not immune. Critics might argue that it will take more radical approaches to fully elucidate and disembed these motives, which have had a deeper influence on biomedicine's ontology, epistemology, and practice than is often acknowledged, setting the field on a course towards increasing technology-driven reductionism and interventionism. This is an area where philosophers can continue to make important contributions.

Overall, *Malignant* is clear and accessible, and it provides relevant insights for a wide audience. For clinicians, the book occasions a second look at evidence used to support treatment decisions and draws attention to conflicts of interest and rhetoric that have the potential to distort findings. For caregivers and patients, Prasad offers tools to better understand and evaluate treatment recommendations and helps to foster appreciation for why hope should not give way to hype, which has a propensity to mislead. For policymakers, Prasad proposes an array of recommendations, ranging from simple rules for mitigating financial conflicts of interest to broader legislative changes in drug evaluation and research funding. For philosophers of medicine, *Malignant* also contains important insights. Although the problems are not new, and many philosophers have long grappled with the issues discussed, Prasad combines an impressive knowledge of clinical oncology, research methodology and health policy, well supplemented by original data from his own meta-research programme, which makes a convincing argument for reform in cancer medicine. His scepticism and pragmatism will be welcome to many philosophers, as will his willingness to engage with controversial issues in clear, unapologetic terms—altogether cementing Prasad's position as oncology's leading gadfly.

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