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VINAY PRASAD, ONCOLOGIST AND TWITTER STAR, LOCKED IN DEBATE OVER PRECISION MEDICINE

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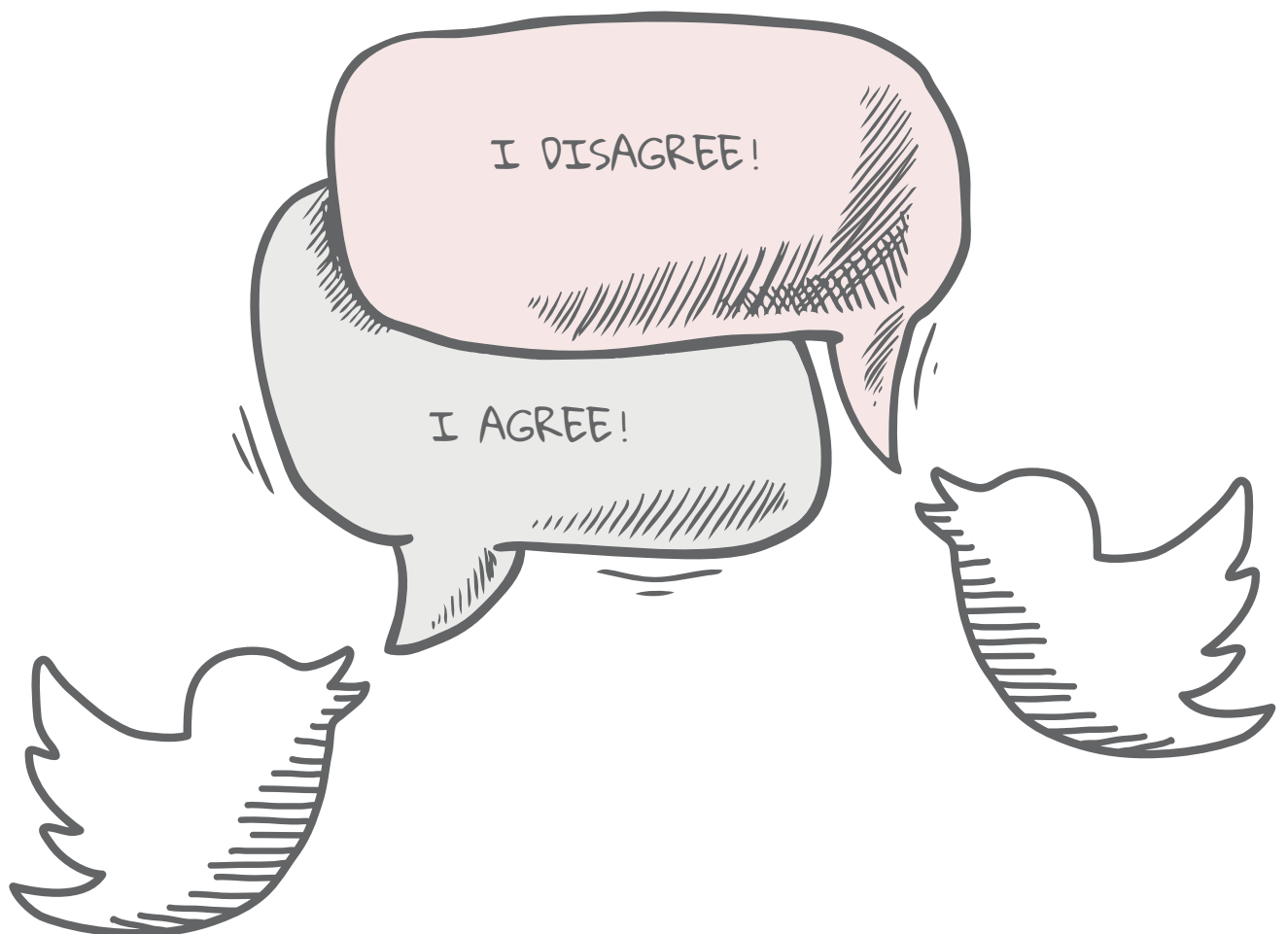
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Vinay Prasad, oncologist and Twitter star, locked in debate over precision medicine

By Paul Goldberg

In recent years, Vinay Prasad, a young hematologist–oncologist at Oregon Health and Science University, has emerged as a premier critic of new directions in cancer medicine.



In his view, cancer drugs are aimed at minuscule populations, approved way too easily, and priced too high.

With nearly 21,300 Twitter followers, over 30,000 tweets, a book, and multiple op-eds, Prasad can turn an academic paper into a bestseller—and an obscure point into a rallying cry.

Vinay Prasad is the guy to call.

An argument can be made that his brand is this strong, because most people in oncology's mainstream, even his biggest detractors, agree with some of his opinions and even make similar points at least some of the time.

This year, the American Association for Cancer Research and the American Society of Clinical Oncology invited Prasad to argue that exaggeration of benefits runs rampant in cancer care today.

At AACR, he was featured at a session titled "[Is Genome-Informed Cancer Medicine Generating Patient Benefit or Just Hype?](#)" The scene was repeated at a "meet the professor" session at ASCO.

In fact, when ASCO was planning that session, there was no shortage of candidates for arguing in favor of precision medicine. However, one name clearly stood out for arguing the "con" side—Vinay Prasad.

"He has positioned himself as the iconoclast/John Ioannidis model for oncology. That was how he floated to the top," said Jeremy Warner, associate professor of medicine and biomedical informatics at Vanderbilt University and ASCO 2018 Annual Meeting Education Committee track leader of the Health Services Research, Clinical Informatics, and Quality of Care track.

Earlier this month, Prasad's publications formed the intellectual foundation of an [editorial](#), "Easier Drug Approval Isn't Cutting Drug Prices," in

Vinay Prasad @VinayPrasadMD

Follow

Agree, I can't read another cardiologist saying orbita runs against their clinical experience. Its a double blind trial. Its better than your experience. Run a positive trial or STFU. You had decades to do so.

David Brown @DavidLBrownMD
Replying to @anish_koka @KLomangino and 7 others

I'm always open to data-based critique. But I'm not open to "I put in stents so only I know how much good they do" because I put them in for 20 years and, other thsn my own anecdotes, I don't know if I did anyone with SIHD any good.

1:21 PM - 23 Dec 2017

25 Retweets 94 Likes

10 25 94

Vinay Prasad @VinayPrasadMD

Follow

Replying to @JParkerMD

Twitter is a new medium that challenges convention. The use of STFU here was cheeky, spicy, and really made the point well IMO. I like it. Here it was directed at an invisible 3rd party, the wall, not 'at someone'. In 2017, arguing about language is the least of our concerns

1:50 PM - 23 Dec 2017

5 Likes

3 5

The New York Times. "Medications are already clearing regulatory hurdles faster than ever, but it's not clear that people, as opposed to drug companies, are feeling much benefit," read the lead editorial in the June 8 issue.

Two of Prasad's opinion pieces—characterized by the Times as "studies"—were cited as key evidence in support of what amounted to a proposal to toughen up FDA's drug approval standards.

Follow the links, and you will see these papers:

- “[Comment](#): Low-value approvals and high prices might incentivize ineffective drug development” in Nature Reviews Clinical Oncology, and
- “[Perspective](#): The precision-oncology illusion” in Nature.

According to his website, Prasad is “nationally known for his research on oncology drugs, health policy, evidence-based medicine, bias, public health, preventive medicine, and medical reversal” and “the author of more than 160 peer-reviewed articles and 35 additional letters or replies in many academic journals.”

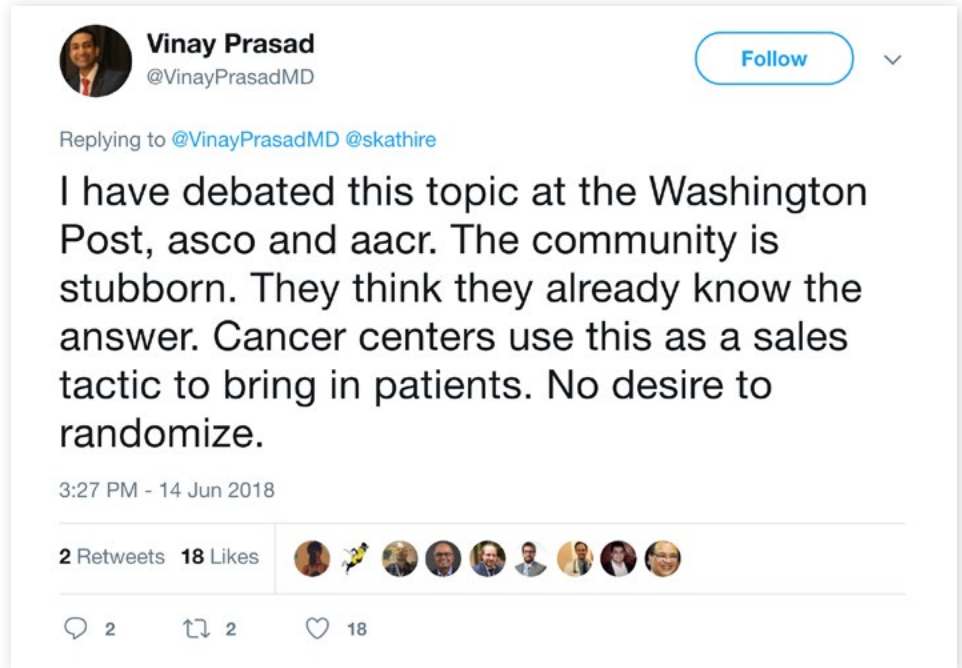
Prasad, 35, is on Twitter a lot, throwing buckets of cold water on work he describes as “boneheaded,” sometimes resorting to name-calling, and using juicy acronyms. In one Twitter post, Prasad demanded proof on usefulness of aspirin in cancer patients: “RCT or STFU,” he declared. RCT, of course, is an abbreviation for a “randomized controlled trial.”

STFU is “shut the fuck up.”

The tweet, dated June 17, 2016, appears to have been deleted during the writing of this story.

“The community is stubborn”

Critics note that some of Prasad’s most tweetable pieces appear on the opinion pages of peer-reviewed journals and that some of these writings are marred by sloppy arguments and less than perfect use of economics and statistics. While the journals are peer-reviewed, opinion pieces are typically only fact-checked by editors and not sent out to outside experts.



Moreover, these same critics say that they don’t wish to meet Prasad on his turf—Twitter.

“Many physicians, myself included, use Twitter as one tool to help keep current on the academic literature,” said David Hyman, chief of Early Drug Development Service at Memorial Sloan Kettering Cancer Center and Prasad’s debate opponent at AACR. “For some others, peer-reviewed papers or, equally commonly, opinion pieces in these journals, seem almost tailor-made for the next Twitter thread.

“This builds a Twitter following, which in turn drives social media citation metrics, now prominently displayed on most journal’s websites, for the next editorial, and so on. It’s a positive-feedback loop. Speed, reductionism, and sensationalism can be incentivized—sometimes to the detriment of more deliberate and nuanced skepticism that has always served an invaluable role in medical debate,” Hyman said.

“As physicians, we all want the same thing—effective and safe treatments for our patients. The disagreement, to

the extent one exists, is really over the best way to get there.”

Prasad’s social media persona is intriguing, said Warner, who debated Prasad at ASCO.

“In terms of social media reach, I don’t know how many of Vinay’s followers are clinicians vs. general public, but his opinions are certainly getting out there way beyond the academic clinical Twittersphere,” said Warner, who directs the Vanderbilt Cancer Registry and Stem Cell Transplant Data Analysis Team. “I was looking at his Twitter feed. It looks like he has made over 30,000 tweets. That is a very time-consuming activity, although not unique amongst the better-known Twitter personas in oncology.”

Recently, in part because of social media stars like Prasad, Warner took a break from Twitter. “It’s hard to get your signal through if other people have such an out-of-proportion presence,” he said. “You see only a few things unless you make it a full-time occupation, which hopefully nobody does. Nevertheless, I still find myself drawn back to

Twitter, as it has become a good venue for news in academia.”

The ASCO debate turned out to be a relatively tame affair, Warner said.

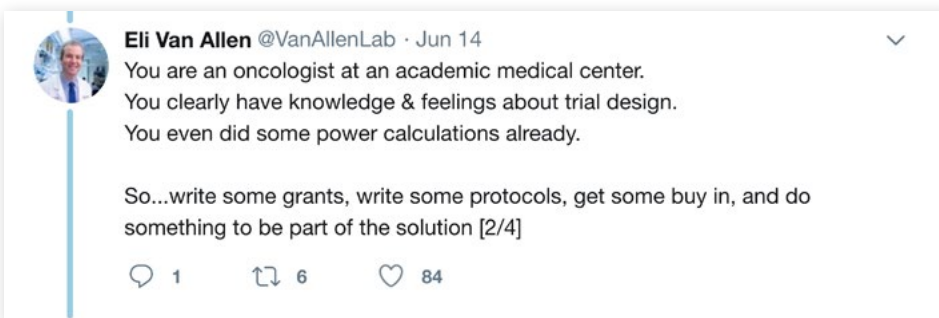
“One of the best comments from the audience, which I agree with, is precision oncology is not just about selecting new treatments,” he said. “It’s about helping to realize that some treatments will not work. It’s not about ‘Let’s choose a new drug.’ Sometimes it’s about, ‘Let’s rationally decide to de-escalate or not to do something.’”

“Prasad didn’t disagree with that.”

Prasad and Warner agree that post-marketing monitoring of therapies in the US simply doesn’t work. And, of course, it’s clear to everyone that precision medicine chips away at niches of cancer patients, some of whom benefit dramatically.

Some of Prasad’s peers wonder whether building a career on criticism of the prevailing system is a sufficient contribution for an academic oncologist.

Recently, Eliezer Van Allen, an assistant professor and translational scientist at Harvard Medical School and Dana-Farber Cancer Institute, posted a [string of responses](#) to one of Prasad’s tweets:



“You are an oncologist at an academic medical center. You clearly have knowledge & feelings about trial design. You even did some power calculations al-

ready. So... write some grants, write some protocols, get some buy in, and do something to be part of the solution.

“Just saying the same thing over and over again, whether in social media or in medical literature, ain’t gonna get it done.”

Prasad responded with a string of [tweets](#):

“I have debated this topic at the Washington Post, asco and aacr. The community is stubborn. They think they already know the answer. Cancer centers use this as a sales tactic to bring in patients. No desire to randomize.”

If his Twitter feed is an indication, Prasad is a man in a hurry. On June 21, he tweeted about having uncovered an apparent scandal involving FDA:

“We often discuss the impact of time to drug approval on patient safety. What about when the FDA takes 6 MORE MONTHS to restrict the use of HARMFUL drugs than the EMA?”

Prasad had proof of the agency’s slothfulness: the European Medicines Agency’s announcement showed clearly that it restricted Keytruda and Tecentriq in bladder cancer on 01/06/2018, while FDA’s documents showed that its restriction went in effect on 6/20/2018.

Presumably, somebody had informed Prasad that in the UK, where EMA is located, 01/06/2018 stands for June

1, 2018, not Jan. 6. FDA was not six months late.

Prasad deleted the tweet.

The magnitude of benefit from precision oncology

I have been tracking Prasad’s pronouncements for a few years, and—like everyone I know—I agreed with some of what I read, and never looked deeply at his argumentation.

The Times editorial changed that. Prasad’s recommendations were being proposed as a basis for approval of cancer drugs.

“The misguided editorial omits many important pieces, including the need for flexibility in clinical trials, particularly for those with serious illnesses,” Friends of Cancer Research said in a statement. “Additionally, the recommendation that FDA should require two successful clinical trials for any drug is rigid, and in some cases, unethical.”

“Arcane rules that tether medicine to a bygone era should not grind our drug approval system to a halt. Such rules will not protect anyone and will only deprive patients of their best chance at recovery.”

With so much at stake for the world’s cancer patients, researchers, and policymakers, it would be important to correct the academic record if Prasad and his colleagues were wrong.

I decided to give Prasad a call.

I had general questions about his thoughts on Twitter, about his views on the FDA standards for drug approval, and—more urgently—I had profound questions about statistical and methodological underpinnings of Prasad’s two opinion pieces cited in the Times editorial.

“Although I tweet about things often, I do not believe I have made any arguments on Twitter that I have not first made in the peer reviewed literature,” Prasad said. “I have some arguments that I purposely do not make on Twitter, because the paper is under review. I’m actually cognizant of that, although I think Twitter is... let’s be honest, why do I use Twitter?”

“Number one, I find it fun. I find it fun to use Twitter, it’s enjoyable, it’s interactive, you get to hear from interesting people. I do not use Twitter to debut ideas, I use Twitter to get ideas out that were published in peer reviewed journals.

“I’m pretty sure that everything I’ve said on surrogate endpoints we’ve already published in a couple of papers.”

During our 40-minute chat, Prasad acknowledged that one of his publications was, in fact, mischaracterized in the Times editorial, when it stated that “according to [one recent study](#), targeted cancer therapies will benefit fewer than 2 percent of the cancer patients they’re aimed at.”

A transcript of that conversation appears on [page 20](#).

In our conversation, Prasad said the percentage of patients likely to benefit is actually two-and-a-half times higher than that. The newspaper “should have just used our [paper in JAMA Oncology](#), where we estimate genomic drugs to be 9 percent, 5 percent responders, I think that is a better estimate, for that particular quote that they’ve used.”

Asked to explain the origin of the 2 percent estimate, Prasad said:

“It depends on the question you’re asking. If the question you’re asking is, of all the people with relapsed tumors who go on NGS, then the answer is two percent. If the question you’re asking is, of all the de novo cancer patients in

America who may benefit from a genomically-targeted drug, the answer is about 5 percent, and that’s our estimation paper in JAMA Oncology that came out last month. I think there are two different estimates. I think these numbers are much lower than what I think many would suspect them to have been. I think they are sobering.”

To put this in perspective, I bounced this comment off MSKCC’s Hyman, Prasad’s debate opponent at AACR.

“This analysis draws an artificial distinction between genome ‘targeted’ and ‘informed’ therapy,” Hyman, a gynecologic oncologist said. “BRCA-mutant breast and ovarian cancer patients who achieve ~60 percent response rates with PARP inhibitors might be surprised to learn they are not benefiting from ‘targeted’ therapy by this definition.

“Response rates, according to RECIST, were also never intended to strictly define the proportion of patients who benefit. An ALK fusion lung cancer patient with a ~25 percent tumor regression (stable disease per RECIST), lasting >3 years probably feels like they have benefited from targeted therapy.

“Ironically, this author has separately published critiques on use of response rate as a ‘surrogate endpoint’ for patient benefit. Instead, I believe this analysis suggests that ~16 percent of advanced cancer patients currently qualify for proven and routine genome-driven therapy.

“Moreover, this estimate does not account for investigational therapies the patient may qualify for on the basis of this type of testing.”

The 2 percent treatment rate cited in the Prasad paper and in the Times editorial came from an early interim analysis of the NCI MATCH trial, for patients with advanced disease. Reported in 2016, these data came from

the first 645 patients screened for ten arms that were open at that time, all targeting rare variants. Today, the trial has 35 arms.

“After accrual of nearly 6,000 patients to the centralized screening phase of the MATCH trial, we found that 19 percent of patients had molecular findings that permitted treatment assignment,” said Keith Flaherty, director of Clinical Research at the Massachusetts General Hospital Cancer Center, professor of medicine at Harvard Medical School, and the ECOG-ACRIN chair of the NCI MATCH trial. “Notably, this excludes the proportion of patients who were not eligible for treatment assignment in MATCH because of prior FDA approval or ongoing late stage trials in patients with those cancer types with those same molecular features. Our experience indicates that NGS testing was an efficient strategy for identifying patients for inclusion in MATCH.”

Zeroing in on Prasad’s “thought experiment”

My conversation with Prasad zeroed in on another of his papers cited in the Times, the “Comment” in the May 18 issue of Nature Reviews Clinical Oncology.

Again, our discussion, which can be read in transcript, triggered profound confusion on my part. A reader is free to blame me, but the fog was failing to lift.

Here is how Prasad’s commentary was described in the Times:

“Drug approval has become so lax and relatively inexpensive, one [recent study](#) suggested that companies could theoretically test compounds they know to be ineffective with the hope of getting a false positive result that would enable them to market a worthless medicine at an enormous profit.”

Running trials of compounds that the sponsors know to be ineffective would be diabolical on many levels.

While Prasad's paper didn't suggest that this was actually happening, it claimed that it was feasible, i.e. that drugs cost so much that a pharmaceutical company could turn statistical errors into profits.

Prasad told me that he was quite proud of that publication, continuing to describe it as a "study."

"I think a thought experiment is a type of study, it's a thought study," Prasad said to me. "In certain fields, some of the studies are purely thought experiments. I think it's a very clever paper. I guess at the end of the day, I think that's a good paper. It's a very good paper, it's a very clever experiment, and I haven't heard anyone articulate anything they think is fundamentally wrong with that thought experiment that would change the conclusion."

Clearly, Prasad is not alone in seeing value in this thought experiment.

Diana Romero, chief editor of *Nature Reviews Clinical Oncology*, wrote in an accompanying editorial titled "To all involved—we have a problem" that the comment by Prasad and collaborators Christopher McCabe and Sham Mailankody represented more than a "moaning exercise" about drug pricing:

"Their conclusion is sobering: any anti-cancer drug that generates a US\$440 million profit and is approved on the basis of the results of a single clinical trial would justify a hypothetical portfolio involving 100 inert compounds.

"This scenario is an exaggerated distortion of reality, and the authors 'certainly do not believe that companies are actively pursuing ineffective drugs', but the revenue they propose actually matches those of many agents currently used in clinical practice.

"Let's not forget that anticancer agents remain the best-selling drugs among FDA-approved therapies (32 percent of sales projected in 2017)². Another fact to keep in mind is that many drug approvals are indeed based on the results of a single trial, which do not always meet the threshold for meaningful clinical benefit³.

"[The authors] state that the risk–benefit balance in oncology clinical trials (regardless of whether they are intended to lead to drug approval) remains to be properly addressed. They do not explicitly formulate a request but, after reading their article, we cannot help but ask for transparency from the regulatory bodies regarding the criteria they use for drug approvals."

age in all journals. The thought experiment was tweeted by 555 and picked up by one news outlet—the Times.

After reading the paper, I had questions about the methodology that went into it.

My biggest question was about the p-value Prasad and his colleagues used in the calculation.

They said that they used a p-value of < 0.05 for how often the inert compounds at the center of their thought experiment would appear beneficial by chance alone. Then, they based their calculations on this p-value equating to the inert compound seeming beneficial by chance 1 in 20 times.

Online attention



Altmetric score (what's this?)

- Tweeted by **555**
- On **2** Facebook pages
- Picked up by **1** news outlets
- **14** readers on Mendeley

This Altmetric score means that the article is:

- in the 99th percentile (ranked 1,335th) of the 205,288 tracked articles of a similar age in all journals
- in the 98th percentile (ranked 1st) of the 53 tracked articles of a similar age in *Nature Reviews Clinical Oncology*

The article's usage metrics, Altmetric score of 307, places it in the top spot among 53 tracked articles of a similar age in *Nature Reviews Clinical Oncology*. Overall, the paper is in the 99th percentile of tracked articles of a similar

This seemed both like very basic statistics, and utterly wrong. Testing two things that are the same against one another will lead to one or the other looking better 1 in 20 times by chance, which means the drug they were hypo-

thetically testing would only look better 1 in 40 times.

When I asked Prasad about this, he told me that their p-value was one-sided—something never mentioned in the publication. And it's not something I have ever encountered in decades of covering FDA.

Other questions about why he left out some costs of testing a drug were answered in equally baffling ways. Why didn't he adjust for inflation when using old estimates of how much a clinical trial cost?

I couldn't follow these answers, and I assumed the readers of The Cancer Letter would also be left more confused than enlightened. So, I decided to borrow a technique routinely used by journals—I put the paper through a process that largely mimics peer review.

First, I wanted to check whether the “thought experiment” had been subjected to peer review at Nature Reviews Clinical Oncology.

“Comment pieces in Nature Reviews Clinical Oncology are topical, authoritative Op-Eds pertaining to scientific research and its ramifications,” Rebecca Walton, a spokeswoman for Nature said to me. “Comment pieces do not typically undergo formal external peer review, but are carefully edited by our in-house professional editors, and undergo fact-checking and copyediting. For confidentiality reasons, we cannot discuss the specific history of any published article with anyone other than the authors.”

Translation: Not as far as we know.

Peer review is a sacred area in science. I didn't want to do anything that might seem unethical or unreasonable.

Perplexed, I called Art Caplan, the Drs. William F. and Virginia Connolly Mitty

Professor of Bioethics at New York University's Langone Medical Center, an expert on ethics in medicine and medical publishing.

I asked Caplan to assess my nascent plan for assessing the value of Prasad's thought experiment. Of course, this would not be formal peer review, but rather a process resembling peer review of the science at the heart of an already-published opinion piece.

“Editors do review opinion pieces, but it doesn't make it a study,” Caplan said. “In peer review, you are given the assignment to make sure the methods justify the conclusion. In an editorial opinion piece, normally the editor is asking: ‘Is this coherent? Does this argument seem to hold together? But that's it. They are what I would call ‘vetted,’ but they are not studies. Signals like ‘comment,’ ‘editorial,’ ‘opinion’ are what journals use to say this is not a study. It could be based on reading other articles and offering your view and interpretation, but it doesn't make it a study.”

I told Caplan that as a reporter, I prefer to keep my sources on record as much as possible, though sometimes I work with unnamed sources. In this case, potential referees told me that they preferred to submit comments confidentially, citing concerns about being accosted on social media.

“I think you can run with anonymous review; I have no issue with that whatsoever,” Caplan said to me. “I have no issue with that, because you know who the reviewers are, you can say the reviewers requested anonymity, you say the reviews are worth publishing, you will be the object of the tweets, and so what? A lot of peer review operates in exactly this way, with anonymous referees. A lot of reviews I get say Referee 1, Referee 2, Referee 3, and I have to trust the editor to have made a selection of reasonable reviewers, because I have no idea who they are.

“Go ahead, these are important matters of policy.”

I decided to keep the authorship confidential, and to publish the critiques. After that, I submitted the critiques to Prasad and his co-authors, and asked one of the reviewers to assess the responses.

I did this with full realization that some journals are starting to move away from anonymous review. However, anonymous review is used by the vast majority of journals.

The assessments of the three reviewers speak for themselves.

The three reviews

All three reviewers agreed with the question I raised about the two-sided p-value. They also pointed out that:

- The thought experiment fails to account for the costs of phase I and phase II trials.
- Also, Prasad et al. seem to confuse revenues with profits, in essence assuming that it costs nothing to run a pharmaceutical company.

The full text of the reviews—with responses from Prasad and his colleagues—appear on [page 11](#).

Here are excerpts from what the reviewers said:

Reviewer 1: Drug profits would... need to be well-north of \$2.5bn per drug to justify development of ineffective agents, about 6-fold the authors' estimate... Maybe we need more transparency about the criteria for drug approval and a suitable, informed debate might well be enlightening. Simplistic, headline grabbing arguments, on the other hand, are not of value.

Reviewer 2: The authors are wrong on what the $p < 0.05$ reflects regarding how often a trial of an inert compound would be 'positive'. They repeat this same error when they talk about the probability of having two falsely positive trials listing it as $.05^2$. They say one in twenty trials would by chance alone be 'positive'. What they clearly mean is that one in twenty trials would show the inert compound to be superior to the comparator. This is a big oops. In testing the null, setting the p cutoff to 0.05 is equivalent to saying you would accept a 'falsely significant' finding (i.e. a Type 1 error) one in twenty times, but those occur half the time when the inert compound appears better than the comparator by chance, and half the time when the opposite is observed by chance. In other words the B term is half the value it should be.

Reviewer 3: Accepting a single trial with a p -value < 0.05 means there is less than a 5 percent probability the finding is wrong due to chance. It is not a 5 percent chance the drug is ineffective or there is a false positive. These are slightly different things that I believe the authors confuse. I am also concerned that lumping 100 trials of different drugs, each with a $p < 0.05$ and assuming 5 findings will be wrong is inappropriate. I am sure that assuming 5 findings will be a false positive is a stretch.

In statements about the cost of drug development and the money made selling an approved drug:

- I worry the authors confuse a drug company's revenue with a drug company's profit.
- I do note a single phase III trial is estimated to cost \$22.1 million in what year? The cost to a drug company for drug development is not just the phase III costs. Is it appropriate to say these costs are "sunk?"

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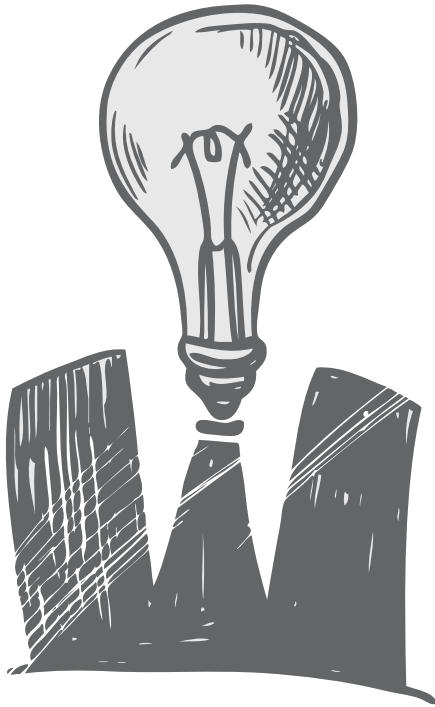
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Reviews of Prasad's “thought experiment”

By Paul Goldberg

As a reporter, I have no standing in settling scientific disputes.

So, when Vinay Prasad and I hit the wall in our discussion of the assumptions he and a group of colleagues made in their provocative “thought experiment,” I decided to do what journals do—send the paper to peer reviewers.

My conversation with Prasad appears on [page 20](#).

The paper in question, “Low-value approvals and high prices might incentivize ineffective drug development” had been cited as a “study” in an [editorial](#) in The New York Times.

“Drug approval has become so lax and relatively inexpensive, one [recent study](#) suggested that companies could theoretically test compounds they know to be ineffective with the hope of getting a false positive result that would enable them to market a worthless medicine at an enormous profit,” the Times editorial states.

If this prospect is real, the world should know. If not, a corrigendum would be called for.

Clearly, the paper, published in Nature Reviews Clinical Oncology, was not a study. It was slugged “Comment.” The journal’s editors said to me that commentary is typically edited in-house.

It is not peer-reviewed by outside experts who have fluency in the subject area. So, peer review, albeit post-publication, would be the paper’s first.

When I approached potential reviewers, several of them cited concerns about being hounded on social media and agreed to participate on condition that their names would not be disclosed. I consulted an ethicist—Art Caplan, at NYU—who reaffirmed to me that this would be consistent with the way reviews are done at journals.

This is not exactly the same as a news publication relying on anonymous sources, which is something The Cancer Letter does on a case-by-case basis. Indeed, we have gone to court twice to protect confidentiality of our sources.

Confidentiality of review in science allows the authors’ scientific colleagues to rise above personalities and, freed from concerns about potential consequences, focus on the truth. Though some journals are starting to identify reviewers publicly, confidential review is still the norm.

Under normal circumstances, peer review is conducted in order to identify concerns and, ultimately, to determine whether a paper should be published. In this case, the goal is to establish publicly whether a provocative hypothesis advanced by the authors and amplified in the Times is, in fact, viable. This

can be determined only by publishing the reviews.

The three reviewers were asked to assess the paper, and their reviews were sent to Prasad and his colleagues. The responses were signed by Prasad, a hematologist-oncologist at the Knight Cancer Institute at the Oregon Health Science University, and Christopher McCabe, executive director and CEO of the Institute for Health Economics in Edmonton, Canada.

After the authors responded, their responses were sent to one of the reviewers to determine whether the authors had addressed the issues.

“Thank you for the opportunity to respond to the post publication criticism of these anonymous people,” Prasad wrote to me after responding to the reviews. “The overall lesson here is that post publication comments are welcome and warranted. I urge these academics to blog, tweet or write letters and we will respond.”

He concluded with a smiley face emoji.

Does the hypothesis set forth in the Prasad et al. paper hold water?

Read on:

Reviewer 1

I have sympathy for the authors' overall thesis that sky-high prices for oncology drugs creates incentives for drug development that may not be in the interest of either cancer patients or society as a whole. However, the authors' specific statistical arguments about the minimum profit required to justify development of an ineffective drug are not supportable.

First, while it is true that 5 percent of trials of ineffective agents will reject the null hypothesis, half of those will favor the control group. Second, phase III trials of completely novel agents without preceding phase II trials are almost unheard of. Yes, the phase III trial of everolimus for hepatocellular carcinoma was conducted without a prior phase II for this specific indication, but there had been numerous prior phase II trials of everolimus, dating back to 2009. Phase II trials typically use an alpha (p-value threshold) of 10 percent. The probability that an ineffective drug will be favored in a phase II and then a subsequent phase III is therefore $10\% \times 2.5\%$ or 0.25%, 20-fold lower than the authors' estimate.

Moreover, the authors' estimate of minimum drug profit for an ineffective agent ignores the cost of either preclinical, phase I or phase II study. Even if we thought that such costs added a mere \$5m, it is clear that the cited estimates are way off.

For instance: start with 400 ineffective drugs, 360 of which fail at phase II for a total cost of $360 \times \$5m = \1.8 billion; 40 phase III trials are then conducted at a total cost of \$880m leading to one marketable drug. Drug profits would therefore need to be well-north of \$2.5bn per drug to justify development of ineffective agents, about 6-fold the authors' estimate.

The statistical lesson to learn from all this is that p-values should not be viewed in isolation. We would indeed have a problem if the data requested by regulatory authorities consisted of a single number on a piece of paper, representing the p-value for the primary comparison in a randomized trial. But as we all know, submissions to agencies

such as the FDA are fat documents including extensive preclinical and early clinical data, and exhaustive details on the randomized trial. Maybe we need more transparency about the criteria for drug approval and a suitable, informed debate might well be enlightening. Simplistic, headline grabbing arguments, on the other hand, are not of value.

Prasad and Christopher McCabe respond:

Thanks for the comments; I will argue the manuscript is not only supportable, but robust & strong. A clearer understanding of cancer trial development, that I will detail, leads to this conclusion.

In the paper, we note that $p < 0.05$ would mean a false positive rate of 1 in 20. This is assuming the p-value is one-sided. The commenter feels that we should use two-sided p-value in which case the false positive rate would be 1 in 40 and our estimate would rise to \$880 million break-even point.

Yet, in the paper we clearly use 1 tailed p-value: first we note that accepting a single trial with a p-value < 0.05 as the threshold of significance means that, if one ran 100 trials for which the null hypothesis were true (that the drug is ineffective), on average, 5 trials would produce false-positive 'statistically significant' results.

The commenter is correct that the above refers to a one-sided p-value. He is also correct that the FDA has required two-sided p-values for some approvals. There is no FDA standard for p-value, one-sided or two sided.

It is important to recognize that no law or regulation requires this (or any other specific) statistical standard to be applied to the analysis of clinical trials (although we have seen that the regulations require a quantitative comparison of the effects of the drug to those of a control group).

(citation)

There are examples for drugs approved based on trials with one-sided (citation) and two-sided p-values and there are examples of FDA approval with false positive rate of 1 in 20 or even higher 1 in 10. (citation)

We look at this paper/thought experiment as exactly that, a thought experiment: What are the potential consequences if the FDA were to be lax and lower regulatory threshold for approval such that drugs with a false positive rate of 1 in 20 or even higher are approved. It certainly does not claim that the FDA approves all drugs in this fashion, and it is clear that the FDA has been even more lax.

[You state]: “Second, phase III trials of completely novel agents without preceding phase II trials are almost unheard of. Yes, the phase III trial of everolimus for hepatocellular carcinoma was conducted without a prior phase II for this specific indication, but there had been numerous prior phase II trials of everolimus, dating back to 2014.”

This is not the right way to think about this. Drug makers have many compounds that have already passed through phase I and II testing, which may have little to no activity in other tumor types. They face the question of how many phase III trials or randomized P2 trials to run. This calculation balances the cost of running the trial, probability of success and expected return. This is what our paper models.

Moreover, there are many other examples of launching phase 3 in cancer medicine based on little early phase rationale. “Many recent phase III RCTs were initiated without sufficient evidence of activity from early-phase clinical trials.”

Kimmelman has shown that after a drug receives approval for one indication it is tested in broad sets of trials in many other tumor types (citation 1 and citation 2) and others have pointed to broad, duplicative portfolios of IO trials (citation) and (citation). It is with this background that we approach our question.

[You state]: “Phase II trials typically use an alpha (p-value threshold) of 10 percent. The probability that an ineffective drug will be favored in a phase II and then a subsequent phase III is therefore $10\% \times 2.5\%$ or 0.25%, 20-fold lower than the authors’ estimate.”

It is simply not factually correct to argue that most phase III trials in oncology were preceded by randomized phase II trials with p-value of 0.1 threshold

From the Tannock paper above, “A recent review showed that a majority of phase II trials evaluating targeted agents are single-arm

studies and that objective response rate (ORR), as used in most phase II trials evaluating chemotherapy, predicts (albeit imperfectly) eventual success in phase III trials (22).

However, ORRs in most phase III RCTs were lower than those in preceding phase II studies, with a mean absolute difference of 12.9 percent (23). There are examples of success with agents that showed a substantial and durable ORR in single-arm phase II trials, including some immunotherapeutic agents, and examples of failures despite showing improvement in OS in randomized phase II studies (24–26). In one analysis more complex randomized, double-blind, and multi-arm phase II trials did not translate to positive phase III RCTs more often than single-arm phase II studies (27).”

Moreover, another paper shows many p3 trials are launched with NEGATIVE or NO phase II at all. 6 percent of negative p3 preceded by no phase II 31 percent only inconclusive p2 and 18 percent a negative phase II study. (citation)

In short, the commentor is factually wrong. We wish we lived in a world where p3 were only launched after positive p2s (that were randomized).

[You state]: “Moreover, the authors’ estimate of minimum drug profit for an ineffective agent ignores the cost of either preclinical, phase I or phase II study. Even if we thought that such costs added a mere \$5m, it is clear that the cited estimates are way off. For instance: start with 400 ineffective drugs, 360 of which fail at phase II for a total cost of $360 \times \$5m = \$1.8bn$; 40 phase III trials

are then conducted at a total cost of \$880m leading to one marketable drug. Drug profits would therefore need to be well-north of \$2.5bn per drug to justify development of ineffective agents, about 6-fold the authors' estimate."

These are sunk costs for our question of what p3 portfolio a company should run.

[You state]: "The statistical lesson to learn from all this is that p-values should not be viewed in isolation. We would indeed have a problem if the data requested by regulatory authorities consisted of a single number on a piece of paper, representing the p-value for the primary comparison in a randomized trial. But as we all know, submissions to agencies such as the FDA are fat documents including extensive pre-clinical and early clinical data, and exhaustive details on the randomized trial. Maybe we need more transparency about the criteria for drug approval and a suitable, informed debate might well be enlightening. Simplistic, headline grabbing arguments, on the other hand, are not of value."

There is no dispute that the current regulatory system is not as bad as our thought experiment, and yet, as we show, the real world is likely not much better, and that is scary and notable. And the title of our paper was "Low-value approvals and high prices might incentivize ineffective drug development", which is fair and accurate and not "headline grabbing"

Reviewer 2:

Thank you for the opportunity to read this paper. I focus just on what the authors term their 'mathemat-

(A: Cost of doing a study) X (B: N of studies to find a lucky positive) < (C: Profits from lucky positive)

Now I will review the errors in each A, B, C.

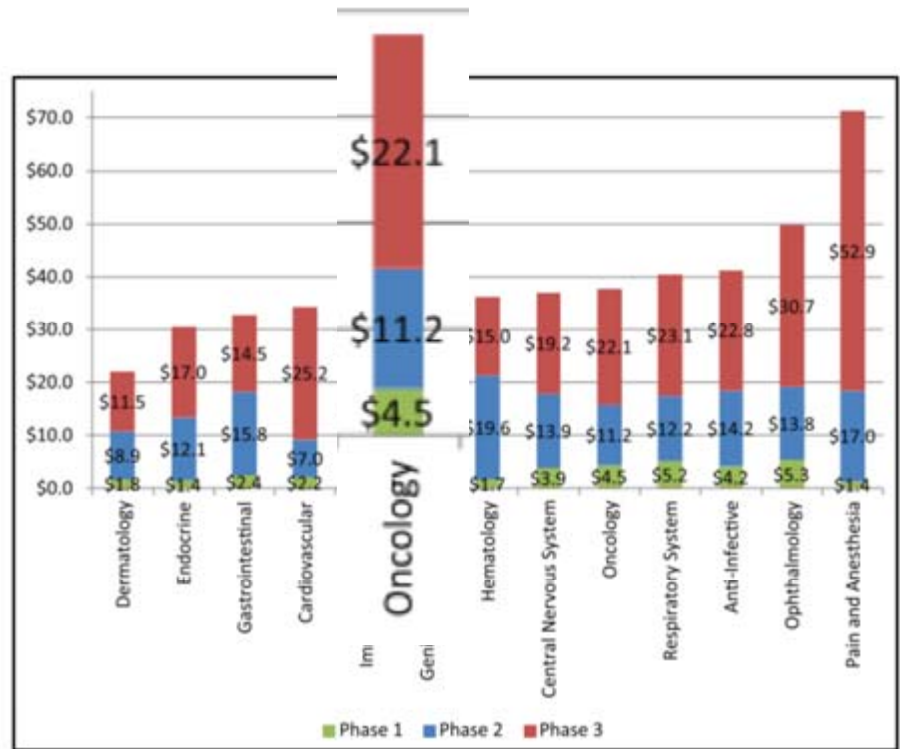


Figure 2. Costs by therapeutic area and phase (in US\$ million).

ical model'. The basic question the authors ask is whether the returns to a company from getting a drug approved are so great that under current cost of development and FDA approval standards, an approach of testing inert drugs would be expected to be profitable. Their answer is a resounding yes, but they seem to have made some problematic decisions that make their thesis more likely to be proven out than contradicted.

Here is the basic equation they are testing and I have labeled each of the components A, B, C

A – Cost of doing the study: The authors rely on a report from HHS on the cost of doing a trial presented for oncology and other specialties separately. The authors however only use the cost of the phase III testing of a compound (\$22.1 million) even though the report includes the cost of phase I and phase II in the same Figure (right, which sum to \$15.7). I see no reason (other than to lowball the cost of testing) to ignore the Phase I and II costs. Another smaller issue is the cost data (2004-2012) they use are older than the company revenue data (2006-2015) by about 3 years or so, and they do not adjust to the same dollar-year. This is a neces-

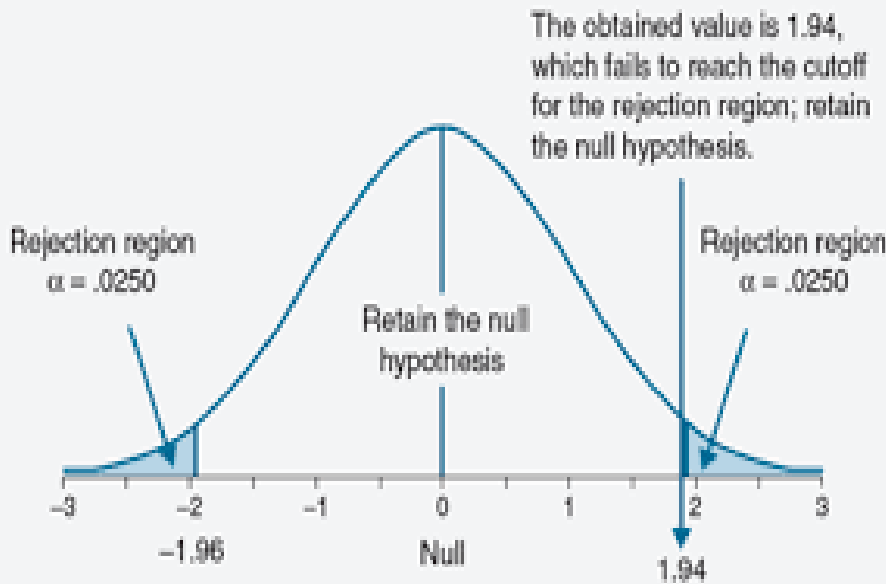
sary step and would bring the two sides of the equation into alignment, for instance raising the value on the left-hand side by around 5 percent. The two fixes would make the A term about twice as large, or thereabouts but when I recalculate below I leave out the inflationary adjustment.

chance. In other words, the B term is half the value it should be.

C – The authors mix up Revenues and Profits. In colloquial language, Revenues are what come in the door, Profits are left over after the company pays the expenses of bringing in those reve-

And here they are talking about how their model shows PROFITS are positive from this strategy:

In short, in the current system, pharmaceutical companies could, hypothetically, turn a profit by testing inert chemical compounds in phase III trials...



Here are some definitions from Investopedia:

“Revenue is the amount of money that a company actually receives during a specific period, including discounts and deductions for returned merchandise. It is the top line or gross income figure from which costs are subtracted to determine net income.”

“Profit is a financial benefit that is realized when the amount of revenue gained from a business activity exceeds the expenses, costs and taxes needed to sustain the activity. Any profit that is gained goes to the business’s owners, who may or may not decide to spend it on the business.”

B – The authors are wrong on what the $p < 0.05$ reflects regarding how often a trial of an inert compound would be ‘positive’. They repeat this same error when they talk about the probability of having two falsely positive trials listing it as $.05^N$. They say one in twenty trials would by chance alone be ‘positive’. What they clearly mean is that one in twenty trials would show the inert compound to be superior to the comparator. This is a big oops. In testing the null, setting the P cutoff to 0.05 is equivalent to saying you would accept a ‘falsely significant’ finding (i.e. a Type 1 error) one in twenty times, but those occur half the time when the inert compound appears better than the comparator by chance, and half the time when the opposite is observed by

chances, like paying for manufacturing, sales people, legal, and CEO compensation.

Here is an example of them mixing up the two terms from their opening explanation of their model:

Third, modern anticancer drugs are highly profitable. In an analysis of ten anticancer drugs that come to the market between 2006 and 2015, we calculated median post-approval revenues of \$1.67 billion at a median of only 4 years after approval.

In no industry are Revenues and Profits the same number (except a kid’s lemonade stand because the parents pick up all the expenses). The industry profit margin is around 30 percent for biotech and 25 percent for pharma (citation). Taking the higher, that changes their term C to 30 percent of 1.67 billion, or \$500 Million.

Here is a quick adjustment of their ‘mathematical model’:

Their equation is:

(A: Cost of doing a study) X (B: N of studies to find a lucky positive) < (C: Profits from lucky positive)

Their values are:

\$440 million (\$22 million X 20 trials to find a lucky positive) < \$1.67 billion, which is True.

Here are more appropriate values:

\$1.56 Billion (\$39 million x 40 trials) < \$500 million, which is False.

Prasad and McCabe respond:

A – The commenter wants us to include phase I and 2 costs. However, as detailed in the prior comment, there is a reason not to include these costs. Drug companies are not running large portfolios of different chemicals, but rather dozens of RCTs of the same drugs, such as Avastin. Thus the early phase costs are sunk, and not relevant to our discussion.

B – The commenter wants us to use a 2 tailed p-value vs. 1 tailed. We clearly use 1 tailed. This is no “oops” but an intentional decision to make the argument lucid and easy to follow. Moreover, I have already established that the FDA is EVEN MORE LAX with approvals, therefore the point is moot.

C – The commenter thinks we have overestimated drug company revenue from drugs, but is missing a major consideration. Drug companies earn \$1.67 billion in revenue in the first 4 years after approval. Here is what is being forgotten. They have 14.3 (10 more) years on average of exclusivity to accrue further profits. (cite: Wang B, Liu J, Kesselheim AS. Variations in time of market exclusivity among

top-selling prescription drugs in the United States. *JAMA Intern Med.* 2015;175(4):635-637.) Assuming no growth in market share (pessimistic outlook), that is 5.4 billion in revenue. It is wrong to multiply this by the profit percent because we are subtracting p3 R&D outlay from the total revenue.

The profit is the balance of the revenue from running an ineffective trial portfolio and the cost.

Moreover, you don't need to depend on this one study. It is well recognized that cancer drugs earn billions of dollars annually ([citation](#)) not to mention far more over their exclusivity period.

Reviewer 3

The hypothesis is a drug company could launch many trials with little chance of achieving success and come out with a profit because one in 20 trials will be a false positive finding.

I am concerned that there is a bit of exaggeration in the paper while there are some legitimate points.

The new definition of cancer using genomics is making many organ cancers into orphan diseases. There are multiple types of adenocarcinoma of the lung, for example.

The FDA realizing that large phase III studies are not possible is accepting small statistically significant improvement observed in single trials as data for approval. In some cases, these studies are not even randomized. This brings up the questions of confidence in surrogate endpoints as well as confidence in the finding from a single trial.

Accepting a single trial with a p-value <.05 means there is less than a 5 percent probability the finding is wrong due to chance. It is not a 5 percent chance the drug is ineffective or there is a false positive. These are slightly different things that I believe the author's confuse. I am also concerned that lumping 100 trials of different drugs, each with a p<0.05 and assuming five findings will be wrong is inappropriate.

I am sure that assuming five findings will be a false positive is a stretch.

In statements about the cost of drug development and the money made selling an approved drug:

I worry the authors confuse a drug company's revenue with a drug company's profit.

I do note a single phase III trial is estimated to cost 22.1 million dollars in what year? The cost to a drug company for drug development is not just the phase III costs. Is it appropriate to say these costs are “sunk?”

The point that low value redundant trials consume a lot of patients, and patients are a valuable commodity is accurate and has been made before.

The original hypothesis may be a stretch, but I do think the argument could be made that a drug company could make money by producing many drugs that have minimal improvement over previous drugs if high prices are charged.

This would protect the drug company from the high investment cost of developing drugs with newer unique mechanisms of action that are more likely to move the needle in terms of effectiveness. In one sobering study, only 19 percent of cancer

drugs recently approved by the FDA met the ASCO definition of clinically meaningful survival outcomes.

In an effort to inform the conversation regarding value and outcomes ASCO published a perspective entitled “Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes.” Ellis LM, Bernstein DS, Voest EE, et al. *J Clin Oncol*. 2014;32: 1277-1280.

Prasad and McCabe respond:

[You state]: “The hypothesis is a drug company could launch many trials with little chance of achieving success and come out with a profit because one in 20 trials will be a false positive finding. I am concerned that there is a bit of exaggeration in the paper while there are some legitimate points.”

Well, we are careful to say, “We certainly do not believe that pharmaceutical companies are actively pursuing ineffective drugs, although the current oncology drug development and regulatory environment does little to discourage such an agenda.”

[You state]: “The new definition of cancer using genomics is making many organ cancers into orphan diseases. There are multiple types of adenocarcinoma of the lung, for example. The FDA realizing that large phase 3 studies are not possible is accepting small statistically significant improvement observed in single trials as data for approval. In some cases, these studies

are not even randomized. This brings up the questions of confidence in surrogate endpoints as well as confidence in the finding from a single trial.”

This is a fine point, but tangential to our paper. Prasad has extensively studied surrogate endpoints in oncology, see here, and related papers. (citation)

[You state]: “Accepting a single trial with a p-value <.05 means there is less than a 5 percent probability the finding is wrong due to chance. It is not a 5 percent chance the drug is ineffective or there is a false positive. These are slightly different things that I believe the author’s confuse.”

I think the commenter is muddying the water. Accepting a 1 tailed p-value of <0.05 means that if you ran 100 inert compounds in RCTs of this size and duration, 5/100 would be positive by chance alone. None of the other commenters dispute this. The p-value is the probability the observed results or more extreme results would have occurred under the null hypothesis. One tailed v two tailed has been the bulk of the dispute.

Ioannidis explains: “Multiple misinterpretations of p-values exist, but the most common one is that they represent the ‘probability that the studied hypothesis is true.’”² A p-value of .02 (2 percent) is wrongly considered to mean that the null hypothesis (e.g., the drug is as effective as placebo) is 2 percent likely to be true and the alternative (e.g., the drug is more effective than placebo) is 98 percent likely to be correct.” (citation)

[You state]: “I am also concerned that lumping 100 trials of different drugs, each with a $p < 0.05$ and assuming 5 findings will be wrong is inappropriate. I am sure that assuming 5 findings will be a false positive is a stretch.”

This concern is unfounded. If you run 100 RCTs of inert compounds per our thought experiment, five will be false positive results with a one tailed p of 0.05. None of the other commenters dispute this, they merely prefer a 2 tailed calculation. Finally, the real FDA is more lax than either standard, thus our argument stands.

[You state]: “In statements about the cost of drug development and the money made selling an approved drug. I worry the authors confuse a drug company’s revenue with a drug company’s profit.”

We mean that the revenue per success justifies the portfolio, and explain above.

[You state]: “I do note a single phase 3 trial is estimated to cost 22.1 million dollars in what year?”

This is based on an HHS report published in 2016. Others may choose alternate figures.

[You state]: “The cost to a drug company for drug development is not just the phase 3 costs. Is it appropriate to say these costs are ‘sunk?’”

Yes, it is appropriate to say that.

[You state]: “The point that low value redundant trials consume a lot of patients, and patients are a valuable commodity is accurate and has been made before.”

Glad we agree.

[You state]: “The original hypothesis may be a stretch, but I do think the argument could be made that a drug company could make money by producing many drugs that have minimal improvement over previous drugs if high prices are charged. This would protect the drug company from the high investment cost of developing drugs with newer unique mechanisms of action that are more likely to move the needle in terms of effectiveness.”

No disagreement. The original hypothesis is a worst case scenario and nevertheless likely to be true, and this corollary, which is closer to the real world, is almost surely true.

[You state]: “In one sobering study, only 19 percent of cancer drugs recently approved by the FDA met the ASCO definition of clinically meaningful survival outcomes. In an effort to inform the conversation regarding value and outcomes ASCO published a perspective entitled “Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes.” Ellis LM, Bernstein DS, Voest EE, et al. J Clin Oncol. 2014;32: 1277-1280.”

We are well aware of these data, and they support our thesis.

Reviewer 2 responds to all comments by the authors:

I have reviewed the authors' responses, and they are in many cases incomplete.

In response to all three reviewers noting that they had made an error regarding how many trials would be falsely positive based on a p-value < 0.05, the authors now state that they meant a one-sided p-value of < 0.05. I see nowhere that this unusual choice was clarified in their paper, and there is no debate that p-values at the 0.05 level are conventionally two sided. The authors say they clarified that they used a one-side p-value by saying that 5 out of 100 trials would be falsely positive in their analysis.

An alternative read of this sentence is they made an error in the first instance in understanding the p-value distribution, and simply restated their error using 5 in 100. It is sort as if someone submitted paper claiming that $7+1 = 10$, and all reviewers said that in fact they sum to 8, and the authors say ‘we expect our readers to know we are writing in Base 8.’

One of the authors' justifications of their unusual one-sided p-value is the claim it makes the paper more lucid and easy to follow. I would think using conventional p-values would be more in keeping with that objective, and I do not think 1 in 40 false positives is any harder to follow than 1 in 20 false positives.

But it is clear that the one-sided p-value works in favor of their hypothesis.

In order to justify excluding the costs of phase I and 2 studies the

authors say now they are focusing just to those companies with existing vast portfolios of compounds that have passed through early testing, and so they can ignore the costs those companies took to get to that point.

This proposed business plan would not get far in any first-year class, portfolios of tested compounds do not just fall out of the sky. If the authors are serious about evaluating a business model of testing inert compounds, they need to account for the cost of getting those inert compounds to the point of testing.

Perhaps by coincidence, perhaps not, assuming earlier phases are costless works in favor of the authors' hypothesis.

The authors do not address why they mistook revenues for profits. They seem to say that basically the two are the same, which is false. Their argument here is that profits are simply leftovers from revenues after accounting for the cost of phase 3 trials.

I am sure many pharmaceutical CEO's would be ecstatic if that were anywhere close to correct. Industry wide, the average cost per dollar of revenue is between \$.70 to \$.75. This means for each dollar in sales the company 'keeps' \$0.25 to \$0.30. Industry average costs on R&D are only \$0.16, there are a lot of other costs. Netting out R&D in the most optimistic case would make the profit margin 36 percent, reducing their 1.67 billion to \$600 million, and in fact because the authors would not net out the cost of earlier testing the \$600 million is on the high side.

Here, too, mistaking revenues for profits favors the authors' hypothesis.

Q

&

Prasad spoke with
Paul Goldberg, editor and
publisher of The Cancer Letter.

A



CONVERSATION WITH
THE CANCER LETTER

Prasad: FDA has confused merely approving drugs with making the world a better place

“

I think it's a very clever paper. I guess if at the end of the day, I think that's a good paper. It's a very good paper, it's a very clever experiment, and I haven't heard anyone articulate anything they think is fundamentally wrong with that thought experiment that would change the conclusion.

”



Vinay Prasad

*Assistant professor of medicine at the
Oregon Health and Sciences University*

I have been following Vinay Prasad's work for several years, agreeing with some of what he said, but never quite finding time to look carefully at his argumentation.

This changed on June 8, when The New York Times published an editorial based in part on Prasad's opinion pieces. The editorial argued that FDA is approving drugs too fast and on too little data, thereby benefiting drug companies, but not the cancer patients.

Prasad's papers were cited incorrectly as studies. However, one of them was slugged "Comment" in Nature Reviews Clinical Oncology. The other was labelled "Perspective" in Nature.

The time had come to give Prasad a call.

I had general questions about his thoughts about Twitter, about his views on the FDA standards for drug approval, and—more urgently—I had profound questions about statistical and methodological underpinnings of the two opinion pieces cited in the Times editorial.

Paul Goldberg: I've been reading your work, but I'm really calling primarily because of The New York Times editorial, which refers to you a couple of times. Are you basically in agreement with it?

Vinay Prasad: I am in agreement with the spirit of it, and with most of it. I thought it was a very provocative and timely and important editorial, and I support the central message here, which is there is a price for less data. Less data for drugs means more uncertainty, and it can exacerbate some of these issues with dealing with price, affordability, access.

I've also been reading your Twitter feed for years. I guess what's interesting there is, it makes me wonder whether Twitter is actually the place to deal with issues like drug approval and endpoints—issues that have been traditionally dealt with in peer reviewed literature.

VP: I guess I would say that, although I tweet about things often, I do not believe I have made any arguments on Twitter that I have not first made in the peer reviewed literature. I have some arguments that I purposely do not make on Twitter, because the paper is under review. I'm actually cognizant of that, although I think Twitter is ... let's be honest, why do I use Twitter?

Number one, I find it fun. I find it fun to use Twitter, it's enjoyable, it's interactive, you get to hear from interesting people. I do not use Twitter to debut ideas, I use Twitter to get ideas out that were published in peer reviewed journals.

I'm pretty sure that everything I've said on surrogate endpoints we've already published in a couple of papers.

I guess I'm just looking at The New England Journal stuff from a couple of days ago. I guess I've beaten up on The New England Journal every now and then, as has probably every reporter at some point.

It was sort of interesting, you're referring to these folks as "boneheads," urging people to tweet at the journal instead of writing letters.

VP: I must clarify one thing: I referred to their analysis as "boneheaded," but I did not ever refer to the individuals as "boneheads." And I refer to their writing is cocky and arrogant, which their writing is cocky and arrogant.

It's hard to argue with that.

VP: That paper is fundamentally flawed. If it were flawed that would be one thing, I would let it go, there are lots of things I read that are flawed, I don't have time to critique everyone, but this is not just flawed.

It will hurt human beings and the combination and the fact that it was published in that journal and it makes a fundamental mistake that now not just I pointed out, Bob Califf and others have pointed out on Twitter, suggest that I really didn't like that paper. It shouldn't have been printed, frankly, it's not the appropriate way to look at phase I response rates.

That's sort of interesting how Twitter is becoming a more common place to air disagreements, probably thanks to our president.

VP: But, also because for years, journals have buried disagreements. They've actively suppressed letters that made provocative points, and that's not just my opinion, but Frank Harrell and Rodney Hayward, who are two very senior esteemed people, have both said the same thing. They feel the same way. Journals have not wanted to publish letters that were very damning to their articles, and now there is a platform where lots of people can read it, and it skips the middle man of the journal.

I think that is a very democratized thing.

Just tweeting at them... But still, drug approval is a very complicated thing. Seeing that being on Twitter makes me kind of scared, but that's just me, I guess.

VP: There are two separate issues. Phase I, I don't think is about drug approval, but drug approval is complicated, I agree. But I think it's nonsense to scientific dialogue, it's also social and political dialogue. The New York Times editorial takes it to a broader audience, and so does Twitter.

It just feels like it drags out sometimes into the gutter, but I guess maybe we've all been too polite too long.

VP: On which topic, drug approval or about bad papers, journal articles?

The way we all discuss papers, the number of characters is just not enough sometimes, for me at least.

VP: I agree, but I think with Twitter you can also thread it, and give tutorials, and visual aids, you can't do that in a letter. A letter is a 150-word limit, that is more restrictive than Twitter or a blog. I actually think the old way of publishing critiques of journals is more restrictive than the new way, where there are no limits to characters. You can just keep tweeting a long stream of tweets. I tend to think it's a good thing that more people can engage.

I think facts do prevail. I think that my tweets are not popular because of the spicy word choice. I think they are popular because I actually patiently explain what I think is wrong. I know that other people sometimes use spicy language, but they do not patiently explain what is wrong with the paper, and they don't get the same reception. This is my view.

Of course. Can we get to The New York Times editorial for a couple more minutes?

VP: Yep.

Your work is cited in a couple of places, do you think it's cited correctly?

VP: The sourced paper is a paper we published in Nature Reviews Clinical Oncology. I would say that first instance is cited very correctly: drug approval has become so lax and relatively inexpensive, one recent study suggests, in a thought experiment, that a company could theoretically test compounds known to be ineffective with the hope to get a false-positive result that would enable them to market a worthless medicine at enormous profit.

I think that is a fair summary of what our paper suggests. In our paper, we are very clear to say we don't think that is actually happening, but that the problem isn't that drug companies are that bad. The problem is they might not be much better. I think that is very accurate.

The second instance, I think is slightly inaccurate, where it said, according to a recent study, targeted cancer studies

will benefit fewer than two percent of cancer patients they are aimed at.

They're citing a paper of mine, where I show that for patients who have exhausted other therapies, if they subject themselves to next-generation sequencing, I estimate that less than two percent of them would obtain a response from sequencing and being paired with a targeted therapy.

That was my estimate in 2015 in Nature, it's slightly different than what they've written. In fact, my estimate was validated by a trial called MOSCATO 01, which appeared in, I believe, CCR. It was exactly 2.1 percent response rate for that population. I think my estimate is accurate.

The way I read the actual piece, you say that 30 percent of the people getting the therapy benefit. I guess I'm a little bit confused about denominators. Do you have to go from the entire population even though those that don't have the mutation? Is it sort of like running a trial of a TB drug, using all infectious diseases as your denominator?

VP: No, that's incorrect. Let's take MOSCATO 01. First of all, that paper's three years old. Now we have the actual study, MOSCATO 01.

Let's look at MOSCATO 01, because in MOSCATO 01 they took about 1,000 people with cancers of diverse histology—these are 1,000 people who in the community would say, "Should I send my tumor to F1CDX? Should I send it to MSKCC Impact? should I send it to MD Anderson? What should I do, should I send my tumor?"

Of that 1,000 people, baseline like 20 percent would be able to be matched with a therapy, about 200, and of that 20, about 10 percent have a response in MOSCATO which is about 20—so about 2 percent of the overall 1,000.

The other 800 people who consented to the study it's a small solace to them that there was no targetable mutation found.

They participated with the highest hopes, so the denominator should be of all the people who subject themselves to sequencing, who desire that sequencing, what percent will end up with drugs that give them a response?

I think that is the only, that's an intention to treat denominator, that's the right denominator.

Of course, any other denominator will inflate the benefits story, excluding many patients in whom there is no match, and that would be deeply unfair to those patients who put their hopes in the test.

If you could explain this to me, how it's not like running a trial for TB drugs and using all infectious diseases as the denominator.

VP: No, it's not that way at all.

In that situation, all infectious diseases—I don't know a lot about TB—but what you're talking about is if everybody with an infectious disease subjected to an intervention... In this case, 1,000 people are saying, "I'm going to get sequenced."

In MOSCATO trial, only about 900 could be sequenced. Of that 200 could be matched with a drug, and out of that, 20 had a response. These people

are actually participating. The denominator is correct.

In fact, that number has been vindicated.

The New York Times, what they've written and this thing you cited are slightly different.

I have another paper that actually is a perfect fit for what they said, but I don't know what to say about this.

I believe that if you participate in sequencing, you are entering into the protocol, you want to have your tumor sequenced. The question is, of all those people who want to have their tumor sequenced, how many people get matched on a therapy and have a response? And that is 2 percent, based on most cocktails.

One could, you could ask the MOSCATO investigators why did they report the 1,000 in their paper in CCR, because that is the true denominator, I think.

Well, at the AACR this year I saw your slide in which you reach a fairly similar conclusion by pooling basket studies, which is sort of interesting. Jose Baselga, said that it would irresponsible to even discuss it, because basket studies shouldn't be pooled. Do you accept his criticism on this?

VP: What is the criticism? That in his opinion they shouldn't be pooled? I think that it is reasonable to pool studies that have been published. What we are doing, we systematically investigated every basket trial that has been pooled, and we asked a different question, which is, "If you enrolled in a

basket study that was later published, what is the average response rate. That's 20 percent?" He's saying you can't pool them, but he's not actually giving any reason why one would not want to pool them.

He's saying that methodologically that shouldn't be done, because...

VP: Why?

Because they were not designed to be pooled.

VP: Similarly, Paul, one could say that to everyone who did a meta-analysis of aspirin, were those studies designed to be pooled? It's in the view of the meta-analyst. When one looks at any type of meta research, the meta researcher decides, could they be pooled or not.

He's not actually giving you are reason. He's using words saying he doesn't like this, but he's not actually providing a reason why he doesn't want it to be pooled. We can disagree about that, but I think this is asking a different question, and this is a fair way to ask that question.

I just wanted to ask about it.

VP: Yeah, I know, I really don't ... he's saying he believes that they are not designed to be pooled. Well, one could say when one did the first randomized trial of statin, one never thought there would be 40 randomized trials of statin, and that randomized trial was never designed to be pooled. And yet the

cholesterol treatment trialists have pooled them many times.

I think it's not a logical thing to say.

I've read a lot of your other papers, and you basically are advocating, in terms of FDA, you're advocating bringing back overall survival or cure as well as standards for approval and also two controlled trials. That's correct right?

VP: No, not quite. I've never said that. That's The New York Times editorial.

OK, so you disagree with that? I just want to establish that, because that's how I've read your work as well; maybe I have misread it.

VP: No, I think, have you read my paper, well, OK then, let me correct you. I guess I would say that I do not believe that two well established trials powered for survival need to be done prior to the approval of all therapies. I do not believe that that is the case.

I believe that surrogate endpoints can be used to approve new drugs. In fact, I have a [paper](#) called, it's an open access paper, it's published in BMC Medicine, and it's with Robert Kemp is the first author.

It's called "[When Should Surrogate Endpoints be Used for Drug Approval and are They Currently Overused?](#)" In my paper, we argue that we believe

that they can be used, and they should be used for drug approval, under certain circumstances, as accelerated approval, with a post-marketing commitment for at least one trial that measures survival and quality of life—in most cases.

We also say the FDA is currently using them too much. I think the nuance here is that it would be easy to say, and incorrect, that I have asked for two trials in all cases prior to approval, that's wrong.

What I'm saying is they are currently overusing surrogates. They're using surrogate for regular approval, where there are no post-marketing commitments, which I believe is a dangerous precedent, especially when those surrogates are unvalidated, and a paper with Chul Kim and I in the [Mayo Clinic Proceedings](#) shows are about a third of the case. That they are unvalidated surrogates used for full regulatory approval with no post marketing commitment, and I disagree with that.

But I do believe surrogates can be used for accelerated approval in certain instances, with post-marketing commitment.

I think the only thing I would say strongly is that, in the current world, in a paper we showed, of 36 drugs were approved based on surrogate, in 4.5 years of followup, only five of them later showed survival benefits.

I guess I would say that 31 drugs on the market for five years with uncertain survival benefits, or quality of life benefits, I think that is a bit too high, out of 36. I think that we could do a better job of providing that information.

Maybe I should ask about specific examples: which of these drugs—I'm going to give you a list—would you pull off the market, given the lack of demonstration of statistically significant overall survival and QOL in, say, two well-controlled studies.

Let's say Gleevec for CML—stays or goes?

VP: I guess I would say that's not really the purpose of these papers. The purpose of these papers is to outline a different regulatory framework for how we can move forward. Gleevec for CML obviously stays, because it's a life-changing therapy.

But I think that one has to realize that there are ways drug regulations could be improved. These are broad ways, that doesn't mean that, how could I put it: You have to have these rules laid out at the outset of drug approval to make really systemic changes. You can't go retroactively and start pulling drugs off the market.

I'd actually don't support that. I think we have to have clearer standards moving forward and move forward with a shared understanding. Nobody wants the rug pulled out from under them in the middle of a situation.

You can't change the rules midstream, you have to change them slowly for future drugs, I think that is what I would say. Going forward, I think we need to think about this more carefully.

Gleevec has been around for decade, but within that decade they did show survival; right? It's actually validated. What about something like crizotinib for ALK-positive lung cancer?

VP: I guess I would say that I would not want to go through specific drugs and say should they pulled or yanked. I'm kind of put out a better regulatory framework going forward.

OK, that's fair enough. I'm wondering about randomizing, in which case, in some cases, I'm just looking at the ethics of it. If you're running a randomized trial of say a BRAF inhibitor in melanoma, would you want to randomize to dacarbazine and a disease progression would you want to cross that patient over to a BRAF inhibitor? How would that impact OS?

VP: They did such a trial called [BRIM 3](#).

But that's not with the dacarbazine, was it?

VP: It was B vemurafenib vs dacarbazine.

Right now, would you do that kind of a trial?

VP: Right now? No, I wouldn't do it right now.

I would say that moving forward, I believe that the majority of anti-cancer drugs could be subjected to randomized controlled trials at the outset. I think it's a different question about what to do about drugs that have already been approved under a variety of circumstances.

The particular drug you are referring to vemurafenib was approved based on a randomized controlled trial called BRIM 3, which was talked about extensively.

Sure, I really should've made it more clear about going forward vs. what happened then.

VP: There are many drugs that we could do more randomized trials for at the outset, prior to approval.

I'll give you an example: atezolizumab in bladder cancer. Second line was approved on a 13 percent response rate in an uncontrolled study. I think that is something that you could have done the randomize control at the outset. Atezolizumab vs standard of care at the outset. I don't think there's lacking equipoise, given a 13 percent response rate with an immunotherapy. But that was not the case, it was approved based on a response rate, and now we have a negative study.

I think we could do some more randomized trials at the outset. We could also measure survival and quality of life sometime in the life cycle of the drug trial; it doesn't always have to be at the outset, but it has to be at some point, I think.

Could we get back again to The New York Times editorial, because it cites your work. This is going to be a really long question, I'm really sorry. Here's what they cite the work saying, "Drug approval has become so lax and relatively inexpensive that one recent study suggests that companies could theoretically test compounds they know to be ineffective with the hope of getting a false-positive result that would enable them to market a worthless medicine at enormous profit."

I guess, first I'm not really sure it's fair to call this a study, right? This is more of a calculation that you've done; right? You called it a thought experiment.

VP: Yes, it is a thought experiment—yes.

But a study?

VP: Is a thought experiment a study? I don't know. I think a thought experiment is a type of study, it's a thought study. In certain fields, some of the studies are purely thought experiments. I think it's a very clever paper.

I guess at the end of the day, I think that's a good paper. It's a very good paper, it's a very clever experiment, and I haven't heard anyone articulate anything they think is fundamentally wrong with that thought experiment that would change the conclusion.

I can walk you through the thought experiment, if you would like.

I would love to do that, but can I walk you through the thought experiment because I'm having a difficult time understanding the p-value and the false positives rates. If I can just sort of explain that, where my confusion lies.

You say that to make this calculation, first, we note that accepting a single trial with a p-value of less than 0.05 as the threshold of significance means that if one ran 100 trials for which the null hypothesis were true and the drug was ineffective, on average five trials would produce false positive statistically significant results. I'm looking at this and I'm thinking, "Wait, this is a two-sided cut off."

VP: No, that was one-sided p. If you want two sided then it would be 2.5, and that would be \$880 million, and answer will still be true.

I thought it would be one in 40 then?

VP: You're saying two-sided, but I think, I'll give you an example that's actually in a second that will make this very clear, but I will say this: In our paper, we use a thought experiment of a one-sided p-value of a .05. If you would prefer, Paul, we can use a two-sided, for the sake of this phone call in which case I would say that would be one in forty, and that would change our esti-

mate to \$880 million, but we've already proven in our paper that it's about \$1.7 billion in profits.

Our conclusion would still be true, but I would say to you that I think our estimate is better for the following reason: olaratumab, which is a drug approved in sarcoma, was approved on the basis of a clinical trial where there was a two-sided p-value of .2, which is equivalent of a one-sided p-value of .1 which is double of what we actually put in our paper, which would lower our value to \$220 million.

[Editor's note: this study was actually a phase II approval study, Prasad's analysis focuses on the p-value cutoff for phase III studies. The sponsor won an accelerated approval on PFS, which allowed them to look at overall survival, as stated in the package insert. A confirmatory trial is ongoing.]

I would say there is a track record of the FDA using even a more permissive p-value than the one we use in our paper, which is olaratumab, in that Lancet Oncology paper.

I would say that somebody might want us to have used a two-sided p-value, but we chose the one we did, because it's a nice way to illustrate it. The truth, the real world, is that we're even more permissive than what we supposed in our paper.

The other thing I say to you is, why stop with two-sided p-value, Paul? You could push it, you could say what if one were to look at the fact that all clinical trials partition a p-value over many looks, you could look at the data many times.

If you partition the p-value in that way, one might reach a slightly different

number. I think our conclusion in this paper is fundamentally strong and sound, and that it is profitable with these assumptions. It would be profitable with these assumptions. In fact, we have an example of it, even more lax approval, which is olaratumab.

Still, the other half is the false-positives that are actually statistically significant negatives, which means that the drug appears statistically worse than the standard of care by chance.

I'm back on the p-value because I'm stuck on the p-value. You're saying that you come to both ends of the p-value distribution because you know of a, there is an example where the p-value is actually worse.

VP: Yes, the power calculation is even... it's exactly right.

In that specific case?

VP: Yeah, in that specific case. All one needs is to say is this: a bar is only as low as the lowest thing that crawls over the bar. The person who wins the limbo is the person who limbos beneath it—that's where the bar is.

I guess I would say that I like this idea of two-sided. I think it's clever; I mean we thought about it when we did it.

We could use a two-sided p, and it would be \$880 million, if you want. It's a different thought experiment. What I think the true thought experiment is what is actually happening in America, which is, that we had approved a

drug that had a two-sided p-value in the power calculation of .2, which is a one-sided p of .1, which would be twice, or—one half of our...—which is twice as permissive as the one we used in our hypothetical, which would give you half the number.

I would say that our number is good.

Just looking at those numbers in the paper again, I guess I'm still confused a little bit, because in your assumption on the cost of testing each drug, you note that the HHS report provides and estimated cost of conducting a single phase III trial in oncology at approximately \$22.1 million. In the same reference, the key cost drivers chose that a stacked cost of cancer drug approval is at \$37.8 million across all phases of study.

VP: But you can't look across all phases.

Why wouldn't phase I and phase II matter? These are costs.

VP: No, but it's the sunk cost. What we're talking about now, we're assuming that drug companies have a portfolio of drugs that made it through early phase testing. We're asking them, we're pretty much trying to explain what you found, which is why do we see so many redundant duplicative PD1 trials? You've already sunk the cost on phase I and II, and now the question is, "Is it worth it to test a PD-1 drug over, and over, and over again?"

The drug companies, the ones that are testing over and over again are Avas-

tin, or nivolumab or pembrolizumab. They're not new drug, new drug, new drug. To that degree, for the purpose of this thought experiment, those kind of costs are sunk, but Paul, let me say just for the sake of argument, let's consider the \$37 million—let's do it.

In our graphic in that paper, you can see there's an X axis that goes—from the top of my head—from 20 to 40. So, \$37 million would fall within that X axis, and you can just move your finger along the line and take the number at \$37 million, if you'd like.

I think that would still be below the average profitability of a cancer drug, so our thought experiment would still be sound.

What about adjusting for inflation here, because you're talking about a report that goes back from 2004 to 2012, and this is six years later.

VP: It was published in 2014 or 16; when was it published?

If you were to adjust for inflation...

VP: Yeah, you can adjust for inflation, but it's still ... adjusting for inflation ... you can adjust for inflation but it won't change the number dramatically.

It would change it from \$37.8 to I believe \$44.4 million per study drug.

VP: OK, but I don't like \$37.8 [million] I like the \$22 because I told you the sunk cost, but then it will go up by a few million, but I don't think it will change the overall conclusion.

OK. Well it doubles it, actually.

VP: That's only if you don't believe...

If I don't believe you should be looking at phase I and II. Right?

VP: And I don't think you should be, because those costs are sunk, as we explain in the paper. You could ask [Chris McCabe](#) about that, because he's the economist that we have as a co-author.

OK, so you do have an economist on that? On the paper?

VP: Yeah, exactly.

The statistics of the thing kind of, the p-value thing I'm still a little bit stuck on that, because it just a fundamental thing.

VP: No, I don't think so. I think that there are, in fact, cancer drugs that use one-sided p values. That's one. For instance, ECHELON-1, I'll give you a trial.

ECHELON-1 used one-sided p-value of .025 in their paper, and you'll see the p-value that got them drug approval was like .04; it's above the one-sided p-value.

The olaratumab is a very strong example. One could look at p-value in perituzumab [in] APHINITY, the adjuvant study—that's also a .047, off the top of my head, something like that.

I would say that one could pick whatever p-value cutoff one wants, but across, I think, a range of reasonable cutoff, and across what the FDA has proven they will approve drugs at, this kind of thought experiment is sound.

That's my opinion, I know everyone doesn't like this thought experiment. People don't like this data, I get it, but, these are the facts.

[Editor's note: I asked Andrew Vickers, a biostatistician and attending research methodologist at Memorial Sloan Kettering Cancer Center, to review the example of ECHELON-1. My question was: "Please help me understand if Prasad is right or wrong here about ECHELON being declared positive even though it did not meet the two-sided $p < 0.05$ cutoff? [Here is the study.](#)

Here is what Vickers said: "He is confusing p-value (what you get from the analysis of data) with alpha (the threshold you compare the p-value to, normally 5 percent). As to the substance of his argument, you can't always derive a decision rule from the sample size calculation. The sample size calculation is a bit odd, because using a one-sided alpha of 2.5 percent gives you exactly the same number of patients as a two-sided alpha at 5 percent. (I'm really not sure why they did it that way). If you use a 2.5 percent cut-point rather than a 5 percent cut-point, then you actually have less power than you planned."]

Is there anything we've missed, anything you would like to focus on?

VP: If you really want to understand about how I feel about this issue, I would start with the article by Robert Kemp and I. Robert Kemp and I wrote an [article in BMC Medicine](#) about surrogate endpoints.

I've gone through it.

VP: We spend five pages trying to really put out what our view is on when they should be used and shouldn't be. I think there are a lot of people who want to distort my position on this issue, and I think that they want to distort it, because they want to create a straw man that's easier to defeat.

The truth is, I've put out, I think, a better proposal than what the current drug approval process is. I've always put out my proposals in the peer reviewed literature prior to tweeting about it.

I've never tweeted a proposal prior to that, except for things like this New England Journal letter thing, which is not really what this is about how we should communicate science and, frankly, I think that is a different sort of thing; it's not FDA drug approval.

I think the letter to the editor is a dead field. I think it's a dead thing and social media has changed that.

I would say about this thought experiment. I think this thought experiment is a very good thought experiment that across a range of different sensitivity considerations one would find this a true thing. What does it really mean? I think it really does explain why we

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I guess I would say that I like this idea of two-sided [p-value]. I think it's clever; I mean we thought about it when we did it.”

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find drug companies willing to spend large amounts of outlay on redundant duplicative trials with low pre-clinical rationale, often for drugs that lack single-agent activity. I think that is a key question.

We have a human welfare problem in the clinical trials system, which is that when you offer a trial of a very low value, you are squandering the scarcest resource that is existing in the system, which are patients.

We have currently incentivized that squandering through bad public policy. That's all we're trying to highlight.

The last thing I want to say, The New York Times should have just used our [paper](#) in JAMA Oncology, where we estimate genomic drugs to be 9 percent, 5 percent responders, I think that is a better estimate, for that particular quote that they've used.

I see, you're talking about in the editorial; it should be about 5 percent response?

VP: It depends on the question you're asking. If the question you're asking is, of all the people with relapsed tumors who go on NGS, then the answer is 2 percent. If the question you're asking is, of all the de novo cancer patients in America who may benefit from a genomically-targeted drug, the answer is about 5 percent, and that's our estimation paper in JAMA Oncology that came out last month.

I think there are two different estimates. I think these numbers are much lower than what I think many would suspect them to have been. I think they are sobering.

I don't think anybody really sees these numbers as especially high, it's just that you have to go through a certain number of patients to find the patients who are likely to benefit. It's a question of denominators. That's really not a surprise.

VP: The reality is that those other patients are people too, and they're people who are not benefiting. My heart aches for them.

What would you propose?

VP: They are being misled by the cancer centers, and the ads, and the rhetoric around it. They're being misled, because they, people are paying out of pocket for F1CDx before this coverage guidance. People have gotten CMS to pay for this, this was not an ideal way to run this research agenda.

When you do find these people who otherwise would not benefit and they do benefit...

VP: That's great! Fantastic!

Would you actually advise a patient to not get tested?

VP: I guess I would advise the patient, I would advise CMS to have conducted that as a randomized study which is what I advised CMS in that paper. Why CMS should run a randomized trial of F1CDx rather than pay for it. We really don't know. You guys have covered PSA screening. Would you really advise healthy men to not get a PSA screening? Well it depends, if a randomized follow-up of PSA screenings showed the benefits then yeah, of course advise them.

If a randomized follow up of PSA screenings showed no benefits, then of course don't advise them, and similarly, if a randomized trial of F1CDx shows a benefit, then of course, advise patients to do it. If a randomized of F1CDx does not show a benefit, then of course not.

The question is, will we ever see such a randomized trial? Who is going to a randomized trial like that? Who will force the randomized trial?

Medicare, when they covered F1CDx, have the legal authority to use a coverage with evidence development rule that said they could have mandated that as a coverage with evidence development. Being that you could get this paid for in the context of an RCT. They did that with a device called Wingspan a few years ago. It actually was a successful thing, it led to a trial that gave us information. They decided not to

do that here. That is the only objection I have.

I've never said "Don't study this," I've never said, "Don't do research on this," I've never said every surrogate is bad. I have always said something slightly different...

There are a lot of surrogates out there and a lot of indications. Looking at the Times editorial—and I know you didn't write it—they're basically suggesting that we go back to the era when there was a survival rule, and when you needed two trials to prove it. I don't think anybody really misses that era, do you? I don't think you do.

VP: I don't think there was ever that era, actually, Paul. If you go back, drugs have been approved based on response rate for a long, long time.

The question now is, when you approve drugs based on surrogates, are those surrogates unproven or validated? Do you have post-marketing commitments or not? Do you enforce them or not? Two Government Accountability Office reports say FDA is not enforcing them for surrogate approval.

Then the next question is, do you use accelerated pathway, where there is a post market commitment or do you use regular pathway, where there is not? They often are using the regular pathway and skipping that. Or the surrogate, they are using many, many surrogates.

They have confused merely approving drugs with making the world a better place, and it's easy to just approve things. It's harder to have knowl-

edge that the things you're approving make actual Americans who are older and frailer and clinical trial patients better off.

That's the question that regulators have to deal with. Do these approvals make the population better off? Do they make average Americans better off? We don't have answers to that, because there are so few, so little data being generated in this space.

The spirit of The New York Times editorial, I think, the spirit is, it's not always about the least amount of data possible, sometimes you need more information. That's a spirit that I think is very important.

Thank you very much.

VP: Thank you Paul, I appreciate it.

Thanks for walking me through this, thanks.

VP: Thank you for asking me tough questions. I would say I think you asked good questions. I really fundamentally disagree with some of them, but I think there is precedent, and I think the p-value thing is wrong, but I made my case and I wish you well.

Thank you so much.

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IN BRIEF



Norman Coleman, Gay Crawford to receive NCCS Stovall Award for advancing patient-centered care

Norman Coleman, associate director of NCI's Radiation Research Program and Gay Crawford, founding director of Cancer CAREpoint, were named recipients of the National Coalition for Cancer Survivorship's Ellen L. Stovall Award for Innovation in Patient-Centered Cancer Care.

Named for longtime CEO of NCCS and three-time cancer survivor Ellen Stovall, who died in 2016, the award aims to honor her memory and advocacy by annually recognizing individuals, organizations, or other entities that are innovators in improving cancer care.

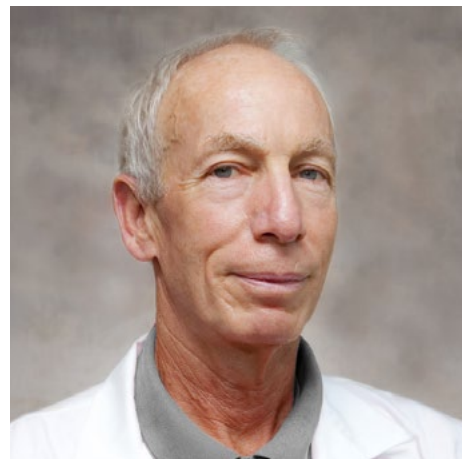
Coleman has been affiliated with NCCS since working with Stovall on the NCAB/Senate Subcommittee to Evaluate the National Cancer Program in 1993. He helped form the New England Coalition for Cancer Survivorship while at Harvard. He is senior scientific advi-

sor to the International Cancer Expert Corps, a non-government organization focusing on global disparities in cancer care.

Crawford has counseled thousands of patients and families over the past 44 years. Some of the programs she helped found include: Hospice of the Valley, the second non-profit hospice in California; Courageous Kids, an American Cancer Society program for children with cancer; the California Cancer Registry; the Colon Cancer Free Zone, advocating for colon cancer screening; and was successful in lobbying the insurance industry to pay for breast reconstructions for patients.

In 2011, she was invited to serve as the first chair of Stanford's new South Bay Cancer Center Patient and Family Advisory Council, helping to develop the program and keep the focus on patient-focused care. In 2013, Crawford founded Cancer CAREpoint, a Silicon Valley based nonprofit organization.

Marc Lippman, breast cancer expert, returns to Georgetown Lombardi



Marc Lippman, a former director of Georgetown Lombardi Comprehensive

Cancer Center, is returning as a professor in the departments of oncology and medicine at Georgetown University Medical Center, beginning July 15.

From 1988 to 2001, Lippman served as director of Georgetown Lombardi. During his tenure, he also served as chair of the Department of Oncology, and professor of oncology, medicine and pharmacology at Georgetown University Medical Center. Lippman joins Georgetown Lombardi as a member of the breast cancer program. He will also establish a laboratory and see patients with breast cancer.

Most recently, Lippman served as deputy director of Sylvester Comprehensive Cancer Center at the University of Miami as well as the Kathleen and Stanley Glaser Professor of Medicine at the University of Miami Miller School of Medicine.

Lippman is known for his work in the investigation and treatment of breast cancer. Before coming to Georgetown Lombardi in 1988, he led the medical breast cancer section of the medicine branch at NCI, and was senior investigator from 1974 to 1988.

Lippman has been issued multiple patents for his work, including several related to the expression of growth factor receptors in tumor cells. He has published over 400 peer-reviewed articles and is editor-in-chief of Breast Cancer Research and Treatment.

Lippman's wife, Nanette Bishopric, is a cardiologist and a professor of medicine at the University of Miami Miller School of Medicine, focusing on epigenetic mechanisms underlying heart failure and cancer. She plans to continue working with Lippman on several cancer projects, and will continue her clinical activities at MedStar Washington Hospital Center and MedStar Georgetown University Hospital.

Laura Hutchins named interim director of UAMS Rockefeller Cancer Institute



Laura Hutchins, a hematologist-oncologist at the University of Arkansas for Medical Sciences who specializes in breast cancer, melanoma and brain cancer, has been appointed interim director for the UAMS Winthrop P. Rockefeller Cancer Institute, effective immediately.

She succeeds Peter Emanuel, who recently resigned after leading the institute since 2007. A committee will be formed to conduct a national search for a permanent director.

Hutchins is a professor in the College of Medicine Division of Hematology/Oncology where she was division director from 1998 until September 2013. She also has served as director clinical research at the Cancer Institute since 1998 and has held the Virginia Clinton Kelley Endowed Chair for Clinical Breast Cancer Research since 2007.

She has been a co-investigator on numerous NIH grants including those focused on detection of circulating

melanoma cells, and using nanotubes to detect and purge circulating cancer cells.

Her research includes collaborating with Thomas Kieber-Emmons, a fellow scientist to study a UAMS-designed vaccine to prevent the recurrence of breast cancer. That vaccine, now in a phase II clinical trial, is being used in women newly diagnosed with breast cancer to determine if the combination of the vaccine and standard chemotherapy improve the benefit of preoperative therapy.

Hutchins was appointed by the governor to the Arkansas Breast Cancer Research Program Oversight Committee from 2001-2004. From 2004-2012, she was appointed to serve on the state Breast Cancer Control Advisory Board, serving as chairman from 2007-2008.

FUNDING OPPORTUNITIES



DOD Prostate Cancer Research Program opportunities

The FY18 Defense Appropriations Act provides \$100 million to the Department of Defense Prostate Cancer Research Program to support innovative, high-impact prostate cancer research.

FY18 PCRP Program Announcements and General Application Instructions for the following award mechanisms are posted on [Grants.gov](https://www.Grants.gov).

Applications submitted to the FY18 PCRP must address one or more of the Overarching Challenges (*revised for FY18*):

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- Reduce lethal prostate cancer in African Americans, Veterans, and other high-risk populations
- Define the biology of lethal prostate cancer to reduce death
- Improve the quality of life for survivors of prostate cancer

<http://cdmrp.army.mil/funding/pcrp>

Health Disparity Research Award

Letter of Intent due Sept. 20

Health Disparity Scholar Award

Letter of Intent due Sept. 20

A pre-application is required and must be submitted through the electronic Biomedical Research Application Portal at <https://eBRAP.org> prior to the pre-application deadline.

All applications must conform to the final Program Announcements and General Application Instructions available for electronic downloading from the [Grants.gov](https://www.Grants.gov) website.

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP



Kymriah shows more than one-year durable responses in relapsed or refractory DLBCL

Novartis announced 14-month results from the pivotal JULIET clinical trial showing ongoing durable responses are achievable with Kymriah (tisagenlecleucel) when administered to adult patients with relapsed or refractory diffuse large B-cell lymphoma.

The overall response rate was 52 percent (95 percent confidence interval [CI], 41 percent - 62 percent), among 93 evaluable patients who were followed for at least 3 months or discontinued earlier. A complete response was achieved in 40 percent of patients and 12 percent achieved a partial response.

Of the patients in CR at month 3, 83 percent remained in CR at month 12, and the median duration of response

was not reached, indicating sustainability of response. These data will be presented in an oral presentation at the 23rd Annual Congress of the European Hematology Association.

In the JULIET study, the relapse-free probability at 12 months after a patient's first response (n=48) was 65 percent (95% CI, 49%-78%). In fact, 54 percent (13/24) of patients who had achieved a PR converted to CR, including two patients between months 9 and 12.

Median overall survival was not reached for patients in CR (95% CI, 17.9-NE). The OS rate at 12 months was 49 percent and median OS was 11.7 months among all infused patients (n=111) (95% CI, 6.6-NE). The median time from infusion to data cutoff was 14 months with a maximum time from infusion of 23 months. At the time of data cutoff, no patients in response following treatment with Kymriah proceeded to stem cell transplant.

Within eight weeks of infusion with Kymriah, Grade III/IV cytokine release syndrome, as defined by the Penn Grading Scale, was reported in 22 percent of patients (14 percent grade III; 8 percent grade IV).

Fifteen percent of patients received tocilizumab for treatment of CRS, including only 3 percent of patients with Grade II CRS and 50 percent of patients with Grade III CRS. CRS is a known complication of CAR-T therapy that may occur when the engineered cells become activated in the patient's body. CRS was managed globally using prior site education on implementation of the CRS treatment algorithm. No deaths due to cerebral edema were reported.

In this analysis, 12 percent of patients had grade 3/4 neurologic adverse events, which were managed with supportive care. Grade III/IV cytopenias lasting more than 28 days, grade III/IV infections and grade III/IV febrile neutropenia occurred in 32 percent, 20 percent and 15 percent of patients, respectively.

Analyses to better characterize and predict severe CRS and neurologic events, including relationships with baseline clinical and laboratory parameters, dose and cellular kinetics will also be presented.

Fifty patients discontinued before infusion and the majority did so due to rapid progression of their disease or deterioration in their clinical status reflecting the acute and progressive nature of r/r DLBCL. Twelve out of 165 (7.3 percent) enrolled patients could not be infused due to inability to manufacture an adequate dose of CAR-T cells.

In May 2018, FDA approved Kymriah for the treatment of adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma based on data from the JULIET study.

Kymriah is not approved for the treatment of patients with primary central nervous system lymphoma. The European Medicines Agency is evaluating the Marketing Authorization Application for Kymriah for the treatment of children and young adults with r/r B-cell acute lymphoblastic leukemia and for adult patients with r/r DLBCL.

JULIET is the first multi-center global registration study for Kymriah in adult patients with r/r DLBCL. JULIET, led by researchers at the University of Pennsylvania, is the largest and only globally conducted study examining a CAR-T cell therapy in DLBCL, enrolling patients from 27 sites in 10 countries across the US, Canada, Australia, Japan and Europe, including Austria, France, Germany, Italy, Norway and the Netherlands. In 2012, Novartis and Penn entered into a global collaboration to further research, develop and commercialize CAR-T cell therapies, including Kymriah, for the investigational treatment of cancers.

Lonsurf improves OS in metastatic gastric cancer

Taiho Oncology Inc. and Servier announced clinical data from the pivotal phase III trial (TAGS) evaluating Lonsurf (trifluridine and tipiracil, TAS-102) plus best supportive care versus placebo plus BSC in patients with previously treated metastatic gastric cancer refractory to standard therapies.

This trial met its primary endpoint of overall survival and secondary endpoint measures of progression-free survival, and safety and tolerability, as well as quality of life. The data were presented as oral and poster presentations at the ESMO 20th World Congress on Gastrointestinal Cancer 2018 in Barcelona, June 20 to 23.

In the TAGS trial, patients treated with Lonsurf had a 31 percent risk reduction of death and a prolongation of their median survival by 2.1 months when compared with placebo (OS of 5.7 months compared to 3.6 months in the placebo group (hazard ratio [HR]: 0.69; 95 percent confidence interval 0.56, 0.85; one-sided $p=0.0003$); at 12-months, OS rates were 21.2 percent in the Lonsurf group and 13.0 percent in

the placebo group. In addition, the risk for disease progression as measured by PFS, a key secondary endpoint, was reduced by 43 percent (HR: 0.57).

Any Grade 3 or higher adverse events (AEs) occurred in 80 percent of treated patients who received Lonsurf and in 58 percent of treated patients who received placebo. Grade 3/4 hematological AEs in patients treated with trifluridine and tipiracil included neutropenia (38 percent), leucopenia (21 percent), anemia (19 percent) and lymphocytopenia (19 percent). Of the 38 percent of patients who experienced grade 3/4 neutropenia when treated with Lonsurf, six (2 percent) experienced febrile neutropenia. No new safety signals were observed for Lonsurf in the TAGS study.

“We intend to include these data in an sNDA submission to FDA for consideration as a third-line treatment option for appropriate patients with metastatic gastric cancer,” said Martin Birkhofer, senior vice president and chief medical officer of Taiho Oncology.

Lonsurf is currently indicated in the United States for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy and, if RAS wild-type, an anti-EGFR therapy.

Greater levels of vitamin D associated with decreasing risk of breast cancer

Higher levels of vitamin D are associated with decreasing risk of breast cancer, according to researchers at University of California San Diego School of Medicine who conducted an epidemiological study published in the June 15 online issue of PLOS ONE.

The study was conducted in collaboration with Creighton University, Medical University of South Carolina and GrassrootsHealth, an Encinitas-based nonprofit organization that promotes vitamin D research and its therapeutic benefits.

Researchers pooled data from two randomized clinical trials with 3,325 combined participants and a prospective study involving 1,713 participants to examine the association between risk of female breast cancer and a broad range of serum 25-hydroxyvitamin D (25(OH)D) concentrations, which was chosen as the marker because it is the main form of vitamin D in blood.

The data were collected between 2002 and 2017—all women were age 55 or older, and the average age was 63. Participants were free of cancer at enrollment and were followed for a mean period of four years. Vitamin D levels in blood were measured during study visits.

Over the course of the combined studies, 77 new cases of breast cancer were diagnosed for an age-adjusted incidence rate of 512 cases per 100,000 person-years.

Researchers identified the minimum healthy level of 25(OH)D in blood plasma to be 60 nanograms per milliliter, substantially higher than the 20 ng/ml recommended in 2010 by the Institute of Medicine, now the National Academy of Medicine, a health advisory group to the federal government. Some groups, such as GrassrootsHealth, have advocated higher minimums for health blood serum levels of vitamin D, as much as 50 ng/ml. The matter remains hotly debated.

“We found that participants with blood levels of 25(OH)D that were above 60 ng/ml had one-fifth the risk of breast cancer compared to those with less than 20 ng/ml,” said principal investigator and co-author Cedric Garland,

adjunct professor in the UC San Diego Department of Family Medicine and Public Health. Risk of cancer appeared to decline with greater levels of serum vitamin D.

Multivariate regression was used to quantify the association between 25(OH)D and breast cancer risk, with the results adjusted for age, body mass index, cigarette smoking and intake of calcium supplements, said first author Sharon McDonnell, an epidemiologist and biostatistician for GrassrootsHealth. “Increasing vitamin D blood levels substantially above 20 ng/ml appears to be important for the prevention of breast cancer.”

Garland, who has previously studied connections between serum vitamin D levels and several types of cancer, said the study builds upon previous epidemiological research linking vitamin D deficiency to a higher risk of breast cancer. Epidemiological studies analyze the distribution and determinants of health and disease, but it has been argued that they do not necessarily prove cause-and-effect.

“This study was limited to postmenopausal breast cancer. Further research is needed on whether high 25(OH)D levels might prevent premenopausal breast cancer,” Garland said. The population was also mainly white women so further research is needed on other ethnic groups.

Diabetes diagnosis later in life may signal early pancreatic cancer in African-Americans and Latinos

African-Americans and Latinos who are diagnosed with diabetes after age 50 are at increased risk of developing pancreatic cancer, according to a

study from the Keck School of Medicine of USC.

Each year, more than one million Americans are diagnosed with adult-onset diabetes mellitus, also known as type 2 diabetes. The diagnosis comes with a long list of potential complications: high blood pressure, nerve damage, kidney disease, stroke, glaucoma and more. But for African-Americans and Latinos, a diagnosis of diabetes after age 50 may also come with a more than threefold risk for developing pancreatic cancer, according to a new study led by the Keck School of Medicine of USC published today in the *Journal of the National Cancer Institute*.

“There are very few studies on diabetes and pancreatic cancer that include Latinos and African-Americans,” said the study’s lead author V. Wendy Setiawan, associate professor of preventive medicine at the Keck School. “Both groups have a high rate of diabetes, and African-Americans, in particular, have a higher risk of developing pancreatic cancer relative to other racial/ethnic groups. Because most people with pancreatic cancer are diagnosed at a late stage, the five-year survival rate is low—about 8 percent. Identifying people who are at high risk early on could potentially save their lives.”

Symptoms of pancreatic cancer typically present when the disease is in its later stages, and no screening methods currently exist.

Using prospective data from approximately 49,000 African-Americans and Latinos, the researchers found that people who were diagnosed with diabetes between the ages of 65 and 85 were more likely to develop pancreatic cancer within three years as compared with people without diabetes.

The data showed that Latinos were four times more likely to develop pancreatic cancer within three years of a diabetes diagnosis, and African-American

icans were three times more likely. The research team also looked at whether late-onset diabetes was associated with breast, prostate or colorectal cancer, and no association was found.

“What we found is that, yes, diabetes is associated with pancreatic cancer in African-Americans and Latinos, but we also discovered that there is a different type of diabetes here, a late-onset diabetes that’s associated with developing pancreatic cancer within 36 months. The evidence suggests that late-onset diabetes may be an early sign of pancreatic cancer,” Setiawan said.

Late-onset diabetes may be a useful marker for pancreatic cancer, she said, providing an opportunity to screen high-risk groups with new tools such as liquid biopsy, which is a test that looks for cancer cells or DNA from cancer cells in the blood.

Study finds emergency colon cancer surgery performed on weekends more likely to lead to complications

The likelihood of severe complications after emergency colon cancer surgery is significantly higher over the weekend, according to a study in the latest issue of *JNCCN – Journal of the National Comprehensive Cancer Network*.

The study examined 5,052 patients who underwent emergency colon cancer surgery at any Dutch hospital between 2012 and 2015, plus another 172 emergency rectal cancer surgery recipients. It found, after adjusting for case-mix, that weekend surgeries had a 66 percent higher mortality rate, and a 29 percent higher severe complication rate, compared to Monday surgeries.

The study, "Weekend Effect in Emergency Colon and Rectal Cancer Surgery: A Prospective Study Using Data From the Dutch ColoRectal Audit," was led by Perla Marang-van de Mheen of the Leiden University Medical Centre, Netherlands, and funded by the Dutch Cancer Foundation.

The researchers used data from the Dutch ColoRectal Audit, which contains a wide range of information on patient and tumor characteristics, treatment, and complications. Planned surgeries were omitted from the study, and weekends were defined as Saturday and Sunday, plus any national holidays. Severe complications were defined as any post-operative complication that led to a hospital stay of more than 14 days or required an additional operation. Of the 5,052 patients who underwent emergency colon cancer surgery during the study's time period, 4,244 (84 percent) were carried out on a weekday, versus 808 (16 percent) during the weekend.

The published results include a call for more research, particularly regarding how care is organized across various hospitals during the weekend, not just for the pre-operative period, but also for post-operative care. These results are probably due to "a far more complex interplay between different factors, regarding both the patient and the organization, rather than simply the day of the initial surgery itself," said Dr. Marang-van De Mheen.

"Allocating appropriate resources during weekends and holidays is critical to achieving outcomes that are just as good on the weekends as they are during the workweek," said Steven Nurkin, associate professor in the Department of Surgical Oncology at Roswell Park Comprehensive Cancer Center, and a member of the NCCN Clinical Practice Guidelines in Oncology Panel for Colorectal Cancers. "The authors should be commended on a very timely study. These results are concerning,

and need to be seriously considered. However, I think we need to be careful in extrapolating just from this study that surgical patients have significantly worse outcomes on the weekends. The weekend on-call teams are there for those true emergencies, and the 'urgent, but not emergent' surgeries may be delayed until the early workweek. Those that get operated on during weekends are frequently 'the sickest of the sick' and are therefore at higher risk of complications and worse outcomes."

"Regardless of whether surgery takes place on a weekend or during the week, it's always important for patients to report any symptoms right away, to make sure that hospital staff has all the relevant information needed to catch complications early on," Marang-van De Mheen said.

DRUGS & TARGETS



FDA to review BRACAnalysis CDx sPMA as companion diagnostic for Talazoparib

Myriad Genetics Inc. said FDA has accepted its supplementary premarket approval application for BRACAnalysis

CDx to be used as a companion diagnostic with Pfizer's PARP inhibitor, talazoparib. The New Drug Application for talazoparib has been granted priority review by the FDA and has a Prescription Drug User Fee Act goal date of December 2018.

Myriad's sPMA and Pfizer's NDA submissions are based on results from the Pfizer-sponsored EMBRACA trial, which evaluated talazoparib versus chemotherapy in patients with germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer. The primary results of the study were presented at the San Antonio Breast Cancer Symposium in Dec 2017.

Myriad estimates there are approximately 125,000 patients with metastatic breast cancer who would immediately qualify for the BRACAnalysis CDx test, followed by 60,000 new patients per year on an ongoing basis.

BRACAnalysis CDx is an in vitro diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes using genomic DNA obtained from whole blood specimens collected in EDTA.

Single nucleotide variants and small insertions and deletions are identified by polymerase chain reaction and Sanger sequencing. Large deletions and duplications in BRCA1 and BRCA2 are detected using multiplex PCR. Results of the test are used as an aid in identifying cancer patients with deleterious or suspected deleterious germline BRCA variants who may be candidates for a PARP inhibitor. This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located in Salt Lake City.

China's drug agency approves Opdivo for previously treated NSCLC

Bristol-Myers Squibb Co, said the China National Drug Administration has approved Opdivo (nivolumab injection) for the treatment of locally advanced or metastatic non-small cell lung cancer after prior platinum-based chemotherapy in adult patients without EGFR or ALK genomic tumor aberrations.

This is China's first and only PD-1 inhibitor and is the only immuno-oncology agent to demonstrate a survival benefit compared with chemotherapy, based on data from the pivotal phase III CheckMate -078 trial, in which 90 percent of the patients enrolled were Chinese.

The approval is based on results from the phase III CheckMate -078 trial of Opdivo vs. chemotherapy among patients with previously treated NSCLC, findings from which were presented at the American Association for Cancer Research Annual Meeting in April 2018.

In November 2017, the trial was stopped early because the independent Data Monitoring Committee concluded that Opdivo demonstrated superior overall survival compared with chemotherapy. The application later received priority review by the Center for Drug Evaluation in China.

In CheckMate -078, Opdivo reduced the risk of death by 32 percent versus chemotherapy, the primary endpoint (HR 0.68; 97.7% CI: 0.52 to 0.90; $p=0.0006$), in patients with previously treated NSCLC. Both efficacy and safety of Opdivo in this patient population were consistent with the results of the landmark global CheckMate -017 and -057 studies. In CheckMate -078, Grade

III/IV treatment-related adverse events occurred less frequently with Opdivo versus docetaxel (10 percent vs. 48 percent). Discontinuations due to Grade III/IV TRAEs were also less frequent with Opdivo (3 percent) than with docetaxel (5 percent).

CheckMate -078 is a phase III, multinational, randomized study comparing Opdivo with docetaxel in the treatment of patients with Stage IIIb/IV NSCLC whose disease has progressed after platinum-based doublet chemotherapy.

The study was conducted primarily in China, with additional study sites in Hong Kong, Russia and Singapore. The trial randomized 504 patients (451 from China, 45 from Russia, 8 from Singapore) without EGFR mutations and with both squamous and non-squamous NSCLC, across PD-L1 expression status of $<1\%$ and $\geq 1\%$, to receive either Opdivo 3 mg/kg intravenously every two weeks ($N=338$) or docetaxel 75 mg/m² intravenously every three weeks ($N=166$) until documented disease progression or unacceptable toxicity.

The primary endpoint was overall survival, including OS consistency observed with the global CheckMate -017 and CheckMate -057 studies. Secondary endpoints included objective response rate, progression-free survival, time to treatment failure, efficacy across subgroups, rates of treatment-related adverse events, and rate of disease-related symptom deterioration, as measured by the Lung Cancer Symptom Scale.

Minimum follow-up was 8.8 months. Median OS was 12.0 months in the Opdivo arm and 9.6 months in the chemotherapy arm (HR 0.68; 95% CI: 0.52 to 0.90; $p=0.0006$). Improved OS with Opdivo versus docetaxel was observed in patients with squamous (HR 0.61; 95% CI: 0.42 to 0.89) and non-squamous (HR 0.76; 95% CI: 0.56 to 1.04)

tumor histology, and across all pre-defined subgroups based on tumor PD-L1 expression level.

The hazard ratios in patients with tumor PD-L1 expression $\geq 1\%$ and $<1\%$ were 0.62 (95% CI: 0.45 to 0.87) and 0.75 (95% CI: 0.52 to 1.09), respectively. The ORR was 17 percent with Opdivo versus 4 percent with docetaxel. Median duration of response was not reached in the Opdivo arm versus 5.3 months in the docetaxel arm. Opdivo decreased risk of disease progression by 23 percent versus docetaxel (HR 0.77; 95% CI: 0.62 to 0.95; $p=0.0147$).

Natera, Institut Jules Bordet to collaborate on neoadjuvant breast cancer assay

Natera Inc. announced a research collaboration with the Institut Jules Bordet, a multidisciplinary cancer reference center in Belgium, using the company's Signatera research-use-only circulating tumor DNA assay to evaluate molecular response and minimal residual disease in women with early stage breast cancer.

Natera will analyze approximately 300 plasma specimens prospectively collected and banked from 80 patients diagnosed with non-metastatic breast cancer, who all received neoadjuvant chemotherapy followed by surgery, and who were then monitored for recurrence with serial imaging.

The study will correlate results of the Signatera assay with clinical outcomes, including pathological response and event-free survival. With sample collection initiated in 2011, the study is led by Michail Ignatiadis, attending physician in the Medical Oncology Department of Institut Jules Bordet and assis-

tant professor at the Université Libre de Bruxelles.

This is the third breast cancer collaboration Natera has announced in the past 18 months. Breast cancer is the second leading cause of cancer death in women in the United States. While the overall survival rate for breast cancer has improved, recurrence remains an important clinical concern, with 5-year recurrence rates estimated to be as high as 33 percent.

Signatera is the first ctDNA assay custom-built for treatment monitoring and MRD assessment. The Signatera methodology differs from currently available liquid biopsy assays, which test for a panel of genes independent of an individual's tumor.

Signatera provides each patient with a customized blood test tailored to match the mutations found in that individual's tumor tissue, which maximizes sensitivity and specificity. Signatera also allows researchers to track additional mutations of interest, up to several hundred mutations, for clinical studies.

In a recent study, the Signatera customized ctDNA assay demonstrated the method's ability to detect residual disease, measure treatment response, and identify recurrence up to 11 months earlier than the standard of care for early stage non-small cell lung cancer.

Additional research presented at the 2018 American Association for Cancer Research meeting showed successful results from bladder and colorectal cancer studies, including median detection points of ctDNA that were 4.3 and 7.9 months ahead of clinical relapse detection, respectively.

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