

Rationally Speaking #153: Dr. Vinay Prasad on, “Why so much of what we 'know' about medicine is wrong”

Julia: Welcome to Rationally Speaking, the podcast where we explore the borderlands between reason and nonsense. I'm your host, Julia Galef, and with me is today's guest, Dr. Vinay Prasad. Vinay is a hematologist/oncologist and an assistant professor of medicine at the Oregon Health and Sciences University. He's also the co-author along with Dr. Adam Cifu of the book, *Ending Medical Reversal: Improving Outcomes, Saving Lives*.

The book treats the question of why is it so often the case that an established consensus in the field of medicine about how to treat a certain condition or a certain disease gets overturned after many years of being used when rigorous studies shows that it has no effect or is even in some cases harmful. Why does that happen and what can we do about it?

That's what we're going to be talking about on today's episode. Welcome to the show, Vinay.

Vinay: Thanks so much for having me.

Julia: Just to give our listeners a sense of what a medical reversal looks like, could you give an example or two of some of the big reversals in recent years?

Vinay: Sure. Let me first put it a little bit in context.

I think maybe myself and maybe many of the listeners, the way we initially conceptualize medicine was the sort of thing where for many years doctors do something, and it's pretty good. It's a treatment that works. Then, something comes along, a breakthrough, a discovery, and we come up with a new treatment that actually works even better. So many of us have this idea that medicine is a series of what we call replacements, something better comes along.

Adam and I had been noticing over the years a disconcerting pattern that a bunch of the things we had recommended, that we had advocated, and we tried to encourage our patients to undergo, they turned out not to be replaced by something better but rather to be no better or worse than a prior standard of care or doing nothing.

Some seminal examples are: one of the things we used to do in the 1990s was for women who had passed through menopause, we would prescribe hormone therapy for those hormones that were elevated prior to menopause. We did that with the hopes that we'd decrease cardiovascular disease.

What it turned out was in a well-done, randomized control trial that came out in the early 2000s, what we found was we actually *increased* the rate of heart attacks by doing that. Here was an intervention that we thought would improve an outcome that actually worsened that outcome. So that's one example.

Another example we talk about in the book is the use of stenting for stable coronary angina. That's the kind of symptom you get when you shovel the snow and it comes on predictably with shoveling, it happens at the same frequency it's always happened, that kind of chest tightness.

This was actually a large portion of cardiac stenting in the United States which is the placement of a small, expandable metal tube in the coronary artery to open up a little blockage. This was 12 billion dollar a year industry, and people had it done, patients had it done, and doctors believed that we were saving lives. Then, a well-done, randomized trial showed us that actually it didn't improve survival, and it didn't decrease the risk of a future heart attack, which were two of the reasons why people thought we were having it done.

Julia: How long were each of those recommended treatments in play before the study came out showing them to be ineffective?

Vinay: At least a decade for those two, and then we have many examples in the book and in some of our work. We find that things that were practices that existed for decades were contradicted, and then even things that cropped up and then were contradicted a few years later. There's quite a range.

Julia: Can you get a handle on the relative frequency of medical reversals? Are the two examples you gave relatively rare, or how common are these cases?

Vinay: You're asking the first question that the reviewers asked of us when we started doing this work maybe in 2010. They said that, "You know, you've got some great examples, but, you know, overall, reversals are rare. They're like earthquakes in California. They make the news, but they don't happen all the time."

Julia: Right – and that they shouldn't necessarily change the way we practice science.

Vinay: That's what some people contended, but I would argue that even though earthquakes are rare in California, we do have a building code that meets earthquake standards, so we are prepared. We're prepared for rare events.

We visited a couple of ways to try to estimate the frequency of medical reversal, and we've done one of them. I can just describe the other two real quick. One estimate was done by The British Medical Journal, and they looked at a set of over 3000 medical practices. What they looked at was of all these medical practices, 3000 things doctors are doing day in and day out, what percent are based on really strong evidence, what percent are based on no good evidence, either way? Then, what percent are really blatantly contradicted?

They found that probably about a third of practices were really based on robust evidence. They found about 15% of what we were doing has really been contradicted, but yet we haven't abandoned it. They found about 50% of what we're doing, there's just no data for.

With that kind of backdrop, we did an investigation several years ago, and then we expanded it a couple of years later. What we did was we looked at all of the articles that appeared in one medical journal, The New England Journal of Medicine, in a decade. There were over 2000 of them. We pulled out the articles that tested the standard of care. There were about 1300 of them. We found out that not surprisingly the majority of articles in The New England Journal test something new. That was about 1000 articles.

Of the 300 or so articles that tested something doctors were already doing, that is already in place, we found about 40% of those articles contradicted something doctors were already doing. What we conclude from this, from these two analyses, is that if you put that 50% of things we do day in and day out that have no evidence either way, no good evidence either way, to the test, we think maybe 40% of them would fail, which is a really sizable percentage of medical practice.

Julia: It's very sizable.

I notice I'm not entirely sure in what direction I expect that number to be biased, if at all. Are the practices that get tested and show up in the analysis that you did, are those practices more likely to be things that people have serious doubts about, and that's why they're being tested? And they may be less likely to be effective than the typical practice that's in use?

Or are they maybe *more* likely to be effective, because they're widely done, and that's why it's worth doing a study on them or something else?

Vinay: You're hitting the nail on the head. I mentioned at first 1000 practices were testing something new, and of 1000, 75% of them were positive studies. That's the bias at play in The New England Journal, which is if you've got something new, you've got to show me it's better than what we already have. That's the selection bias.

If you looked at the practices that we're already doing, I would say the mere testing of a standard of care is provocative. It's the sort of thing that people want to know about whether it's affirmative or contradictory. We found 38% were affirmative, which really validated what we were doing, and 40% were contradictory, so it was about an even split.

Now, you're saying is this likely to be a skewed view of the literature? For the reasons you mentioned, one could imagine if either an underestimate or an overestimate. It's hard to know. The true answer is we don't know. What our work has done, and then there's been a bunch of other very related projects, is to show that this is not something that happens really infrequently. This is not a solar eclipse. It's a more day-in and day-out problem in medicine.

Julia: Let's focus first on practices that had some evidence behind them -- maybe not up to the gold standard of evidence, not at the level of the study that was ultimately done that showed them to be ineffective, but we had some reason for doing them other than just that's how we've always done things.

What was going wrong with that earlier body of evidence that caused this practice to seem effective when it wasn't?

Vinay: That's a very good question. Every single practice, whether it was contradicted or subsequently reaffirmed, they all had really sound pathophysiology. They all had a biological explanation, a physiologic explanation, a biochemical explanation for why something should work. Everything had that.

Then, on top of that, there were different layers of non-gold standard evidence, as you point out, such as some things had k-theories -- which was a doctor saying, "Hey, I tried this on 50 people and this is what happened."

Some things had really carefully done historical controlled studies where doctor said, "You know, we did this for 40 patients, and we compared it to the 40 patients before who we didn't do it on, and look how much better these 40 patients did."

Some practices were based on observational studies, which often are large cohort studies where we follow, for instance, several hundred thousand nurses for several decades, and they fill out food frequency questionnaires and dietary questionnaires and medication questionnaires, and we track their different outcomes and their survival. Then, we ask questions like, "Oh, you know, if they took hormone therapy post-menopause, was that associated with better or worse outcome?" They're not randomized studies, they're not experiments, but they're thought to be natural experiments. We think we can control for those covariants, the confounders that vary between the 2 groups, so there's this different hierarchy.

Then, also even in some cases, reversals happened because of a randomized trial. If a randomized trial is small, to this poor endpoint of controls. One of the biggest things we talk about in the book is a surrogate endpoint, which I think we can talk about a little bit more in a bit. Also, if randomized trials are biased in the many different ways in which a randomized trial can be skewed from the outset where somebody could have a thumb on the scale.

Julia: I want to double-click on this, on the problem with surrogate outcomes. Now, I think, is a good place for it. What is a surrogate outcome, and why is it arguably the sort of thing that we should be looking at even if in practice that leads us astray?

Vinay: A surrogate outcome is, as my co-author, Adam Cifu, likes to say, it's something you didn't care about until a doctor told you to care about.

Julia: That's a great definition.

Vinay: It's a great definition. Your blood pressure or your blood sugar or your cholesterol level, it's something that we're taught to care about.

If you really are honest with yourself, what do people actually care about? We care about living longer, living better. We care about avoiding heart attacks, avoiding blindness, avoiding death, avoiding disability. We don't really care about our blood

sugar level. We care about it in so far as we think it predicts these other things, but we don't care about it in and of itself. If somebody told me my blood Z level was a million, I would say, "I don't even know that is, and I don't really care." A surrogate endpoint is any outcome that can be measured easily, quickly, and which we believe tracks with an outcome we actually care about.

In the history of medicine, we've done many, many studies, and we have many whole fields that rest on evidence that we can improve surrogate outcomes, we can lower blood sugar, lower blood pressure, or lower blood cholesterol. In some cases, we also have that evidence saying that, "And it matters, and we improve outcomes people care about." In other cases we don't have that evidence, and in a few cases, we thought we did improve a surrogate, we know we did, but it turned out we didn't improve those outcomes downstream that we actually care about.

Julia: Why might that happen? We do have good reason to believe that, correct me if my medical science is wrong because I do not have a background in medicine, but I think having blood pressure predicts, leads to heart disease. Is that right?

Vinay: Right. Heart disease and stroke and mortality.

Julia: Good, so, a bunch of things that patients care about. If we can show that some intervention, some medicine reduces blood pressure, why would it not be the case that we could just assume from that that it would reduce the likelihood of heart disease and stroke and so on?

Vinay: That's a great point. I will say that the full answer to the question, it's not a completely solved riddle. If it were, I think we could overcome some of the deficiencies. The real root of the question is there are a couple of ways in which we prove surrogates.

One is we look at different groups of people. And it does turn out that people who have naturally lower blood pressure have better cardiovascular outcomes than people that have naturally high blood pressure.

Then, the next question is, "Well, if you lower blood pressure, do you actually lower cardiovascular outcomes?" It turns out that's true for many different classes of drugs, something called a thiazide diuretic or calcium channel blockers. It wasn't so much true for a class of drugs called beta blockers. Then, you get into why some classes of drugs, why some drugs, why not other drugs? It has to do with probably off-target effects.

Julia: What does that mean?

Vinay: Off-target effects, so that the drug may have a beneficial effect on a surrogate but may affect the body in some other way that has a countervailing harm, that is such that it's a net negative. That's one possibility.

Two, that the drug doesn't affect the surrogate long enough. Perhaps it affects blood pressure on a short term, but night time blood pressure spikes. Or perhaps it's not really blood pressure that you're capturing but blood pressure variability.

I'll take an example from my own field of cancer research. We do, even to this day, two-thirds of our drug approvals are based on surrogates. The two surrogates we use are shrinking tumors, and keeping tumors from growing past an arbitrary line 120% their smallest size. That's called progression.

Those are the two surrogates that are behind all of these cancer drug approvals, and yet in many cases we found that you can have a drug that shrinks tumors but it doesn't improve survival -- because perhaps the cancer roars back just as fast as it was growing before.

You can have a drug that delays progression, but it doesn't improve survival, and that may be because the simple fact is that progression is not measured very cleanly. It's based on the visual inspection of a tumor on a CAT scan, and we've done studies where if you give the same CAT scan to 10 different radiologists, they have 10 different opinions about whether it grew or shrank even. There's bias in the measurement.

Measurement error, off-target effects, there are different ways in which the fidelity of the surrogate can be questioned. It's a very important question, and the full answer in every case has not worked out. The take-home lesson is that unless a surrogate is super-well validated, and that's a whole field of statistics in and of itself, unless it's that level of validation, we should be wary about it.

Julia: I'm also wondering how clear-cut an alleged medical reversal really is most of the time. As you already alluded to, even if randomized controlled trials measuring the outcome we actually care about instead of the surrogates, even if those are the gold standard, they're still not perfect. If we have a large body of a bunch of mediocre studies that all suggestively point at an effect, then we do one really well done randomized controlled trial, and it finds no effect, it's not clear to me that that should always cause us to update strongly towards, "Okay, well this is ineffective." How clear cut is a medical reversal?

Vinay: You're raising a good point, and there are certainly situations where, I can just think of an example that comes to the top of my mind, about ways in which we ventilate patients who are critically ill. There was a type of ventilation where we put a patient on their back and then on their front side. It's called prone ventilation, and many studies were done that didn't show a benefit, and we have a recent study that shows a benefit.

It's really in this murky, gray zone where you can call for more studies or you can scrutinize the studies we do have, and there can be some legitimate debate. But what we found in the examples we detail, usually the pre-existing levels of evidence were super-inadequate in comparison to the contradictory study, the reversal study. They were often orders of magnitude smaller.

They were often single center studies which have their own inherent biases like very enthusiastic proponents can drive results. They were not sham-controlled. They were not controlled in many cases.

Then, the randomized controlled trials were often much bigger, better controlled, multi-center, double blinding, all of the design features that help you feel confident that you're actually testing the experimental intervention. If you look through our book, and a lot of different doctors have, there may be a dozen reversals that people may really want to argue about, but the majority of these reversals have been strong reversals in that sense. I am saying it because there's 150 reversals in the book, so even if 10 are debated...

Julia: A related question is: Having a body of prior evidence that consists of bunch of mediocre studies, is one reason you might have a prior suspicion that a treatment is working before you do a rigorous RTC. But another reason you might have this prior suspicion is just a priori reasoning, or "common sense."

This is something that I've thought about, to take a brief digression, because I co-founded this nonprofit, and we run workshops where we try to train people in critical thinking techniques and various other kinds of rationality habits. The hope ultimately – Like, I may think that thinking rationally is an end in itself, but that's just a value that I happen to have. I'm not going to claim that everyone should learn rationality because it's a virtue in itself. Ultimately, hopefully the goal is that it makes people more successful at things they care about, and happier, and it causes their behavior to be better for the world in some way.

Vinay: A utilitarian justification of rationality.

Julia: I won't go too far afield because that's a whole other can of worms, but -- point being there's not a lot of evidence showing that rationality training actually affects these long term outcomes that we care about. In part because it's just very hard to do those studies, and not many people have really looked at the effects of rationality training yet even to the extent that it has been studied.

We did one small RCT a couple of years ago where we had 20 people come to our workshop and 20 people, a statistically identical control group, not come to the workshop. Then, we tested them before and then a year later where the treatment group had come to the workshop and the control group didn't.

We looked at a bunch of outcomes to see if they were different. You might look at, say, money. Does learning rationality make you more effective at earning money? You might think that should be related. It seems like it should be probably, but we found no effect, and-

Vinay: You may be under powered, but, still.

Julia: Yeah, it was a small study. But also the relationship, even if it exists, I would expect it to be a noisy one. I would expect there's lots of reasons even if you become way more rational and more effective at what you do, being more productive, et cetera,

maybe rationality training also causes you to decide that it's not worth it to you to slave away in a high-powered, high-earning job, and you want to do something more fulfilling and earn less money, et cetera. I would expect these relationships to be hard to detect.

Yet, still even though we don't have hard evidence yet, I still have this a priori assumption that probably learning critical thinking and good decision-making skills, it's likely to have positive effects even if we can't yet prove that.

Vinay: Then, here's what I would say. I consider myself an expert on the use of clinical trials when it comes to medical claims, living longer, living better, quality of life, mortality, morbidity, and that's what our book is focused around. I think you're alluding to this fact that what we're getting at when it comes to how you think about causality, how you think about advising people and intervention, why should that just be confined to medicine. In fact, you see recent op-eds saying that, "You know, we need more randomization in social policy or in education research," or things like that. Those are amenable, but you are hitting at this idea that are there some social phenomena that it would be very difficult to even imagine a rational trial's agenda?

In our book, we talk a lot about nutritional science as one of those places where, when you think about the breadth of different nutritional options and all of the permutations that one could have, that really making traction on "an optimal diet for health," it's going to be very, very difficult.

...Then the other thing that we've thought about a lot is drug regulation. We have a whole bunch of rules that govern when drugs come to market, and there's this huge ongoing debate about whether or not those rules err on the side of blocking potentially promising drugs, or do they err on the side of permitting potentially harmful drugs that are ultimately useless?

We argue about that using observational evidence, using different what I would consider non-gold standard evidence, one might start to imagine, "Well, could one do gold standard studies in this field?" Then, one starts to think about all of the incredible difficulties in doing that. If you, let's say, randomize nations to different policies on approving drugs, people may move from one nation to the next or companies may move from one to the other. That doesn't quite capture what that effect that policy would have if it were applied universally. Would companies retool their entire R and D if the bar for drug approval were higher, and actually chase after drugs that have bigger benefit?

Your question gets at that, and it's a very deep question. I can't answer it, and I don't consider myself an expert on that field. It's philosophical. But when it comes to medical questions, I do think the common sense thing is a lot harder, because we've had such a history of so many good randomized trials that have really completely shredded common sense. One example we talk about in the book is, it's common sense that if a patient has multi-drug resistant bacteria on their skin, that going in the room and wearing a gown and gloves and throwing it away before you step out in the hallway that that would decrease transmission, infections, and those kind of things, and-



Julia: I wouldn't even have thought to do a study to test that! It would just seem like a natural application of the basic laws of science as we understand them.

Vinay: Exactly, and it's a natural application of the basic principles of bacterial transmission -- and yet it didn't improve outcomes in now two randomized trials.

What happens is when you start to live under these policies, you may start to see, "Hey, some guy came in to drop off a tray of food, and he may not have worn the gown." A doctor wears the gown but then sits down on the bed, or the doctor wears the gown and the stethoscope comes out and touches the patient. You start to see all these holes in the system.

Then, you think, "Well, maybe the problem is patching the holes." Perhaps the hard thing is to accept the fact that maybe all the holes can't be patched. Maybe you can't even come up with an intervention, that the interventions run so counter to human nature, that it can never be implemented in a way that actually improves outcomes. That's the really pessimistic converse.

Julia: Assuming a medical reversal is basically on the clear-cut side, as you pointed at, how long does it take for that practice to stop being used commonly in the field of medicine?

Vinay: I guess you're alluding to this lag time that we talk about, which is after contradiction before abandonment.

We have anecdotes, like the example of stenting for stable coronary artery disease. When that was really resoundingly contradicted in 2007, there was an initial dip in the use of that procedure. It has since resumed pre-COURAGE levels, levels as before the trial.

There's been one empirical investigation by John Ioannidis who's very famous in this field. He looked at contradicted claims in the literature. One such claim was that beta carotene supplementation could prevent lung cancer. In the 1980s, 1981, there was a really seminal observational study that suggested that that would be true.

By 1993, from '91 to '93, there were three randomized controlled trials that said, "Hey, it doesn't decrease lung cancer, that's for sure." One of the trials said it actually increases lung cancer, but at least it doesn't decrease lung cancer.

John tracked citations to the original beta carotene paper into the future. He hypothesized that, "Look if people were really heeding the contradictory evidence, they would stop citing the original paper." He compared it against the average citation, the paper from that same journal that same year.

He found that actually even 7, 8 years afterwards, people were citing the original '81 beta carotene paper at very high rates. And he looked through those citations, and it's not cited to say, "Hey, look how we got it wrong." It's cited to say, "Look, beta carotene still remains promising." There is a lag time. It's probably around a decade.

That fits with our experience in these very circumstantial pieces of evidence we have. It speaks to the fact that medical practice is a battleship, and it doesn't turn on a dime.

Julia: Well put.

We've indirectly talked about the harms of medical reversal, or more to the point the harms of having a system in which medical reversals are so common, so where the harm is really the practices being used before they're reversed. Maybe let's go into a little more detail about those harms. As you describe in the book, they do extend beyond a practice having turned out to cause direct harm to people's health.

Vinay: Adam and I, we try to keep it simple, and we always tend to say that there's three big harms of medical reversal.

The first harm is all of the people who underwent the practice during the years it fell in favor, they were rightly harmed. In some cases, the harm was merely opportunity cost. Or they wasted some money. In some cases, they experienced the net side effects of the treatment without any countervailing benefits.

The second harm has to do with the lag time you alluded to. Doctors don't change practice immediately, so future patients are harmed for several years, even a decade after a contradicted practice, it's contradicted, but before it goes out of favor.

The third harm is the insidious harm. It's the loss of trust in the medical system. It's the harm that is a really deep harm. We've seen it a couple of times. When the United States Preventative Services Task Force flipped on their recommendation to recommend mammograms to women between the ages of 40 and 50, it created a vicious backlash. The rhetoric that was around it was "government officials want to watch people die just to save a buck." That's the rhetoric, and that's misleading rhetoric because the real reason they did that was because they felt that it doesn't save lives. It's not about the money, it's about the mere question of does it actually work.

Then, we saw it with prostate cancer screening.

It's not just patients who are frustrated when doctors flip flop, it's doctors themselves. It's one thing to take the lessons of reversal to think more clearly about medical evidence, but some people misinterpret their lessons to mean something like "All of western medicine is bad," or "Everything doctors say will always been contradicted. It doesn't matter if it's a randomized trial with 2000 people or if it's an observational study with 10 people historically controlled." Some people draw the wrong lessons from the problem, and that's a deep problem. It's only human nature.

People think that doctors are maybe more objective and methodical than the average person, but I don't think we're any different. We're subject to the same sorts of psychological biases. If you've been doing something for a long time and it's made you money and you thought it did good, and it turns out that somebody tells you one

day that it doesn't work, you're going to have this huge internal conflict about that. You're going to resist changing.

Julia: If you've seen even a few examples in which it seemed to work, even if that's not a statistically significant result, having seen it with your own eyes, having done that with your own hands, feels more compelling than reading the result of an abstract study. I find.

Vinay: Absolutely.

Julia: Even for me, even knowing that, the anecdotes are intuitively more compelling.

Vinay: Even talking to people who are like-minded, when I punctuate something with an anecdote about, "Well, let me tell you about one patient I had who had a prostate cancer screening exam and look what happened to him." It has so much resonance, even in people who have been trained to think dispassionately about evidence.

Julia: So let's say now, if you had your druthers, if you were the king of the world or the king of medicine at least, and you could reallocate the way we're doing things or the way we're spending our resources... When people ask me how I would change -- usually I'm talking about social science research, because that's what I know about. But the way that I always feel like I would want to change social science research is that I would take the resources we're currently spending on social science research, most of which I think is going to studies that are basically useless, and that we can't really update at all from their findings because of the way they were done.

And I would just reallocate it to a much, much smaller number of studies, that are focused on the cases where we can actually measure the outcome we care about in the real world. How people make purchasing choices, say, in the real world as opposed to a game that an economist set up in a lab at a university with undergrads. Limit ourselves to studies that are as long term as we need them to be, that have a control group, and all those good things.

Those would certainly be more expensive. And also there would be fewer cases in which they would even be possible, but at least those-

Vinay: They would be more informative.

Julia: Exactly. And overall we'd still be able to update much more from that tiny group of well-done studies, than from the giant group of studies that are currently being done with the same resources.

I'm wondering if that is something you could endorse as a change to deal with the problem of medical reversal as well? If not, what you would recommend?

Vinay: That is a perfect analogy to the situation we have with new drugs, where we do clinical studies for idealized efficacy, where we take people who are perfect otherwise than the disease in question. They have no other co-morbidities, they

have no other medical problems. They're not on any medication. We give them the drug under really idealized circumstances. We carefully monitor them. They're often decades younger than the average person with their problem. Especially in cancer. And we ask if the drug actually improves survival or something like that. That's what it takes to get approved.

I've been a big proponent for: that's the wrong way. The question is, once the drug is approved and we're giving it to people who are 10 years older and have real comorbidities, does it work the same way? If it has only a marginal benefit in idealized, what we call a clinical effectiveness research -- or research that actually informs the real world? I'm a big proponent of that.

As you mentioned, it may cost more, but its conclusions will actually have real-world implications rather than idealized implications that speak to no one. I would say, if I were king of medicine -- of course heavy is the head that wears the crown, but -- what I would do is: If we just look at the way that we spend our resources, we're spending 700 billion dollars a year in Medicare spending on healthcare. We're spending probably an additional several hundred billion dollars a year. We're well over a trillion dollars in healthcare spending at 20% of GDP, and what percent do we spend on research? The NIH has a budget of 30 billion dollars, and clinical research or clinical trial research is just a fraction of that 30 billion.

We're spending at most 2% of what we spend on healthcare in knowing whether or not the healthcare actually works. I would dramatically shift that. The percent of healthcare spending that as long as we live in an era where so much of medicine is untested, the percent of medical spending that should be on testing it should be at least 15%, 10%, 5%. I'll settle for 5%. It should be much more.

Clinical trials should be pragmatic, which is exactly what you alluded to. My frustration with social science research, too, is people play a video game in a laboratory, but what does that tell you about real world interaction? The same thing in medicine. People who are 40 years old with metastatic colon cancer, they improve survival by 1 month with some new pill with medium toxicity. When you take that pill and you give it to the average patient who's 75 with colon cancer and who's got heart medication, cholesterol medication, and other medication, and that person has way more side effects. They may not even get that one month at the end. There's very rarely a trial that informs our practice for those patients, so we should have that switch.

Then, we could talk about it more, but in the book we also talk about deeper ways we can try to tackle this problem, reforming medical education, how we train doctors, reforming how we promote professors, reforming the drug and device approval process, and also trying to reform an ethic among people who practice medicine to demand better evidence.

Julia: A lot of things I want to double click on there! First, you just alluded to something, a point I was particularly struck by in your book, which you treat briefly, but it really hit home for me. Which is that the focus in medical education and probably also in pre-med programs is on the science behind the medicine. Organic chemistry, for

example, probably physics as well, that primes people to be compelled by or to be focused on the wrong kind of evidence. Can you elaborate on that?

Vinay: Absolutely. We do toss it out there, and to some degree, it's a hypothesis. I'm not going to say that I've proven it, but there is this sort of dangerous cognitive fallacy that happens in medical training, which is that the entire first two years, you're taught about the mechanism by which a drug will exert action. You're taught that the drug will go and bind this particular receptor in the brain or in the kidney. It will interdict the function. It will downregulate the downstream protein. It will cause an upregulation of this other protein, and that should reverse what we're seeing.

You see that when students come out of the classroom and they start going onto the wards. You ask them questions like, "Why do we prescribe an ACE inhibitor for patients with heart failure?" They start to tell you about angiotensin 2 and downstream TGF beta signaling and ventricular remodeling. You say, "Whoa, whoa stop. The reason we do it is because multiple randomized trials have shown it improves survival, period."

What you're saying is perhaps the putative reason behind why it improves survival perhaps is our best thinking lies to the mechanistic way it works, but that's not the reason why we do it. The reason why we do it is that it works in carefully done clinical trials. That fallacy is present over and over in medicine.

To some degree it is necessary, in the sense that all of us in medicine encounter cases that don't fit any clinical trials, and we have to at least come up with a stab for what we would do. Inevitably we go back to those skills, and we say, "Well, let me think about the biology. Let me think about how this works." That's okay. That's a good way to generate hypotheses.

But the danger comes when you don't check yourself, when you don't say, "Whoa. Let me also remind myself that this is merely a hypothesis and that if this keeps happening over and over in my clinical practice, you know, I better be good about actually testing this in some robust way." We subordinate empirical science, top down randomized trial science, to basic methodological science, and that's behind a lot of these reversals.

Julia: I feel like I've seen the same phenomenon happening in social sciences, but also things like evolutionary psychology. Where an economist will have this theoretical model of human behavior, like a rational agent responding to incentives, or signaling. Or an evolutionary psychologist will have this model of adaptive traits and so on. And they draw conclusions based on those models in almost a mechanistic way, and are not really that interested in sometimes, or moved by, empirical or statistical results if it contradicts the theory.

To be fair to doctors, the science of physiology or of biology is at least somewhat more of a science than economics or evolutionary psychology. But maybe not as much more as people assume?

Vinay: You're right on that people, they get comfortable in the model, and then they forget to say that the core of science is not to develop a model but to push the model and ask, "Well, if this model were true compared to other models, what's the testable question that would differentiate the two?" and to apply that test.

That's the hallmark of science. In fact, if you want to make even a bigger argument, the way we teach science in grade school, middle school, even by high school, it's really not science. It's just the rote memorization of models. And it's very rarely thinking about the experiments that prove one model over another model, over another alternative. That was not until for me in college really where we started to see that.

Your question is about to the core is how robust is medical biological science? There are certainly maybe tens of millions of papers in PubMed and millions of laboratory researchers doing work, and many things that do work do have very parsimonious and elegant basic science behind it.

Many things that do work also we have very little idea how they even work at all. For instance, inhaled gases for anesthesia. Even to this day, we really don't know why they knock people out, yet many of cancer drugs are very intelligently designed. The more you study medical history, you just keep seeing the role serendipity plays, in terms of a drug that you thought interrupted one protein. It was given randomly to a bunch of patients, and some other people responded. Then later they started to look, like, "Well, what was it about them that responded?" Then, they discovered a different protein that actually worked on.

That happens in the field of cancer research. There have been many things that have happened that we really have strong pathophysiologic models that we got burned on even in recent years. We try to detail some of that. Even in medicine that has a great evidence base, basic science evidence base, it's still is not robust enough that you can skip those confirmatory studies.

Julia: We're almost just about out of time for this section of the podcast, but I'll close with one more question just to bring things back to the pragmatic level. Talking to our listeners as patients, which we'll all be at some point in our lives, do you have any advice for how we should be making health decisions for ourselves, given this problem that you've detailed?

Vinay: We make a strong case that probably the most important thing you can do is to find a doctor you trust whose maybe fundamental view of life and healthcare is similar to your own view, or at least they get where you're coming from. They get your priorities and desires and goals, and they can work with you and are willing to work with you. You find a doctor who you can ask a lot of questions for.

Then, in fact, if I were to make one very specific suggestion, it would go to the point of your last question. Which is that patients, like early medical students, they gravitate towards the nuts and bolts of how something should work. "Oh, I have a fractured vertebral lesion, and you're going to go with a needle and inject medical-grade cement, and it'll increase the thickness of the bone."

They should be asking the questions of, what's the evidence behind it, how has it been tested? That shifts from going from "how does it work" to "what's the evidence for it". It is a very important shift.

Julia: Excellent. We are all out of time, so I will wrap up this excellent conversation, and we'll move on now to the Rationally Speaking Pick.

[interlude]

Julia: Welcome back. Every episode, we invite our guests on Rationally Speaking to introduce the pick of the episode. That's a book or a website or something else that has shifted their thinking in an interesting way. Vinay, what's your pick for this episode?

Vinay: A book that I read in the last year that really made me think differently about something was *Capital in the 21st Century* by Thomas Piketty.

Julia: Give us the gist of what it's about, and then maybe you can explain how it's influenced you.

Vinay: Thomas Piketty is an economist who cares a lot about patterns of wealth over time, how money has been passed along from generation to generation. For an economics book, it's actually gotten a very broad reading, and it's very clearly readable for someone like myself who's not in the field.

The thing I found very interesting about the book was he's done a lot of careful empirical work in terms of measuring throughout 18th Century England and France how much money was passed along generation to generation, and how much money is earned in each generation.

He has this very interesting quote in the book where he says... [there's] some discussion in Voltaire where someone says, "Is it better to marry rich if you want to become rich, or is it better to have a job that pays you a lot of money?" The joke was, "Well, of course it's better to marry rich. You'll never earn that much money."

He asks, "Well, in what periods of society was that not the case?" It turns out it was very rarely not the case. For most of society, it was in fact true that the largest driver of wealth was inherited wealth and interest on capital.

The reason it made me think a little bit differently is it makes you think about income taxation in the United States. Which is a progressive income tax, which I think is right, but it taxes income and it doesn't tax wealth. Those are different things, and really the thing we want to shift is wealth and equality in the long run. It makes you think about whether or not there's something we should be doing differently from a tax perspective, even if you are progressive like myself, that I had never thought about.

Julia: Excellent. I am well aware of this book, because all the cool kids in my circles were toting it around this past year, and I keep meaning to pick it up. It's just dauntingly dense. But I expect to really enjoy it. I very much endorse its empirical approach to history --

Vinay: That's what I liked about it.

Julia: A nice tie-in to the theme of the episode.

Vinay, it's been such a pleasure having you on the show. Thank you so much for joining us, and we're going to link to your pick but also to your book, *Ending Medical Reversal*, which I highly endorse to all our listeners.

Vinay: Thank you so much for having me.

Julia: This concludes another episode of *Rationally Speaking*. Join us next time for more explorations on the borderlines between reason and nonsense.