

## Episode: Ethics Talk – Could Trusting Science Mean Not Trusting Some FDA Decisions?

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TIM HOFF: Welcome to Ethics Talk, the *American Medical Association Journal of Ethics* podcast on ethics in health and health care. I'm your host, Tim Hoff. This episode is an audio version of a video interview conducted by the Journal's Editor in Chief, Dr Audiey Kao, with Dr Caleb Alexander, a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health, about the US Food and Drug Administration's controversial decision to approve aducanumab for the treatment of Alzheimer's disease. To watch the full video interview, head to our site, [JournalofEthics.org](http://JournalofEthics.org), or check out our [YouTube channel](#).

DR AUDIEY KAO: Dr Alexander, thanks for being a guest on Ethics Talk today. [music fades out]

DR CALEB ALEXANDER: Of course. Thanks for having me.

KAO: So, at a time when trust in science and government has eroded for some, how do you see this decision influencing public confidence in FDA authority and in health care?

ALEXANDER: Well, it's an outstanding question, and it's a complex one to unpack. There's, of course, enormous interest in the impact of this decision on many things, including drug development; the treatment of, the development of new products to treat Alzheimer's; the clinical care of individuals with this common, and often devastating, disease and their loved ones; and also, as you point out, trust in the FDA, in one of the central institutions that governs the market access and the safety and effectiveness of medicines in the United States. So, there are a lot of complex factors at play.

There's a reason that this decision has been in the news and that it has been so closely scrutinized. On the one hand, you have enormous unmet need, an incredible hunger or demand for new products and for treatments for diseases where there have not existed effective treatments. And so, I think the FDA understood that and factored that into their decision. On the other hand, you have a product with very limited evidence and also non-trivial safety concerns. So, while most of the focus has been on the evidence of the product, I think its safety also comes into play. Because, of course, at the end of the day, the choice of a product for a patient depends upon a risk-benefit balance. So, again, I think it's too early to tell the ultimate impact that this decision will have. But there's no question that it's a consequential one, and it's one that will be watched very closely in the months and years to come.

KAO: Given what you just said, some have suggested the FDA's decision was unduly influenced by patient advocacy groups and the drug's biopharmaceutical manufacturer. So, how should the FDA balance these groups' interests and stakes against public health and safety?

ALEXANDER: Well, I think it's an understandable concern on the part of some and that highlights the perennial tension that the FDA faces in often threading the needle and sort of walking the tightrope between, on the one hand, ensuring adequate access to new treatments and fostering innovation, and on the other, maintaining suitable standards of safety and effectiveness. And, you know, the thing that makes this decision stand out so much is that despite what some might say to the contrary, this was hardly a typical application of the FDA's typical standards, evidentiary standards, of approval. So, I do think that the FDA relies on advisory committees and multiple reviewers and review teams and has any number of measures in place to try to navigate this tension between being supportive of industry, supportive of innovation, not unduly hindering access, market access, for new products, but on the other, being sure that there are standards.

And, you know, there's a reason that the FDA is so highly regarded around the world as a regulator. And it's because typically, they apply good, reasonable, rigorous standards and do so fairly well. And again, that's what makes this decision so hard to reconcile with the totality of work that the FDA does, because it really, I think it really does stand apart from the FDA's usual and customary ways of doing business.

KAO: It has been reported also that this medication will cost \$56,000 per year, per patient. So, how should we consider equity as an ethical value in our assessment of this drug's costs and benefits for individuals and for populations?

ALEXANDER: Well, again, a really good question. Of course, it's not the Food and Drug Administration's primary concern, so that's important for people to recognize. The FDA, during the course of their reviews, isn't focused on equity. They're not focused on costs. Those are very important factors, very important matters, but not, sort of not the core of what the FDA's doing. I'm not saying that the FDA is completely blind to those or sort of uninterested in them, but it's simply not their regulatory mandate. But I think that equity is a real issue here.

The cost may well be less than \$56,000 or \$59,000 at the end of the day. But keep in mind, even that cost is head and shoulders above what a very credible nonprofit think tank, ICER, has estimated to be a value-based cost of something like \$2,500 to \$9,000 per year, plus or minus. So, there's a world of difference between those estimates. We know that some patients getting this may have as much as 20 percent out-of-pocket copayments. And even costs of \$10 or \$20 for a blood pressure medicine or a diabetes medicine is often cost prohibitive for millions of Americans. So, to think that there won't be equity concerns is just putting one's head in the sand. And I think that there are going to be, looming large, important questions that have to be navigated regarding who's getting this treatment, who's getting access to it, to whom is it being offered, and to whom is it being offered who doesn't ultimately end up using it because it simply would break the bank.

KAO: So, given what you've just said, how should physicians then respond to patients with Alzheimer's disease who request this medication?

ALEXANDER: Well, I mean, keep in mind this is hardly a sterling product based on what we know now. I mean, this is a drug that has clear and well-defined, non-trivial safety concerns, has unclear efficacy or effectiveness, and costs a bundle. So, it hardly has the features of a product that you would imagine would be adopted like hotcakes. On the other hand, there are many patients and their loved ones that are suffering from Alzheimer's and may believe or may feel that something is better than nothing. And I think that that is an

understandable concern or understandable perspective. I would, as a treating clinician—and I am a clinician—highlight that there are potential risks with the product as well as its potential benefits. But I think that these are questions that are going to have to be carefully navigated by clinicians and patients and caregivers alike in order to reach judgments about when this product is indicated and when it should be used.

KAO: Do you have any thoughts about the FDA labeling for this medication in terms of which population should be using it? Any thoughts on that?

ALEXANDER: Well, I mean, listen. It's been a month of surprises, and I think many of us were shocked that the FDA approved this product. Then to see that it was approved based on an accelerated pathway that posits that amyloid is a valid surrogate was quite a shock. And then more recently still, to see that the FDA label doesn't stipulate that the product be indicated only for individuals that have elevated amyloid levels and have mild cognitive impairment or mild Alzheimer's disease. Those are the individuals in whom the product was studied. And in fact, Biogen, the product's manufacturer, has indicated that they believe that the reason that their product works, or one of the reasons that they believe it works, is because it targets people with early-stage disease. So, to have the FDA or others indicate that this product should be labeled broadly so that anybody with Alzheimer's would have the opportunity to use it simply flies in the face of evidence and the manufacturer's own statements.

There are many chapters to the story that have yet to be written. And one of the most important ones that's looming large is the role that payers, the coverage and reimbursement decisions that will be made around the product. And I think that there's a major opportunity for payers to use the evidence that we have, which focuses on individuals that have documented elevated amyloid levels and early-stage disease in order to guide coverage and reimbursement. And keep in mind, up to half of people with mild cognitive impairment, and up to maybe 25 or 30 percent of individuals with Alzheimer's, don't necessarily have elevated amyloid levels. So, there are individuals in which there'd be no rationale, mechanistically, to think that this product would even have a fighting chance of making a difference. So, I do think that there are a lot of questions that remain, and this question of sort of how narrowly payers and providers and patients and their caregivers can channel treatment selection to those that really withstand some chance of gaining from it is an important one.

KAO: So, as we near the end of our conversation, if you were teaching this FDA decision as a case study to students, what would you want them to learn and take away from it?

ALEXANDER: Oh, there are so many opportunities for learning. I think understanding the basics of the evidentiary standards for market access, the different types of approval pathways that manufacturers can use, the accelerated approval pathway, and it's being posited on a surrogate, and what a surrogate endpoint is, how we know that surrogate endpoints are valid or not. What have we learned the hard way about surrogates that, in fact, are invalid endpoints that we've used in the past, such as, for example, the notorious case of cardiac antiarrhythmics that reduced rates of arrhythmia, but actually increased rates of death when arrhythmias were used as a surrogate. You know, and the ways that the FDA has to navigate various tensions as they regulate products. There's also an opportunity to consider post-approval regulation, right? Because now that the product is approved, there are still obligations that the sponsor has, there are still statutory requirements that the FDA has, and so there's a wealth of opportunities for learning from

this case, hopefully, so as to continually improve and sharpen and enhance the system of pharmaceutical regulation in the United States.

KAO: So, with that, I want to thank Dr Caleb Alexander for sharing his expertise and insights with our audience today. Caleb, thanks again for being a guest on Ethics Talk.

ALEXANDER: Great. Thanks for having me.

KAO: For more COVID ethics resources, please visit the *AMA Journal of Ethics* at [JournalofEthics.org](https://www.journalofethics.org). Thank you for being with us today. We'll see you next time on Ethics Talk. [bright theme music plays]