The following is a transcript of the 2022 Annual Meeting session titled Artificial Intelligence and the Future of Psychiatry. The transcript was submitted by chair of the session, P. Murali Doraiswamy, M.D., who interviewed Califf.

PMD (00:03)

Dr. Califf, it's an absolute honor and pleasure to have you join us at the annual meeting of the American Psychiatric Association. For the attendees in the audience, Dr. Califf is the Commissioner of the Food and Drug Administration. He's actually serving a second stint. He was nominated by President Obama, I believe, in 2015, served his first term starting in 2016, and then went on to have a distinguished career again back at Duke and as a senior health strategy advisor for Alphabet. And now he's back for a second stint as the Commissioner of the Food and Drug Administration. So, my first question to you, Dr. Califf, as one of the most famous physicians in the world, you could have had any job you wanted. What brought you back to the FDA for a second stint?

RMC (00:49)

Thanks, Murali. It's good to be with everybody today. And a lot of people have asked me whether I lost my mind come back after knowing what the job is like. But this is really you know, at age 70, when you get a call from the White House saying “Will you consider coming back?” It's a matter of service and a realization that there's so much at stake right now for future generations and getting things right at this point. There’s lots of turmoil and difficult issues to address. So, it's a good challenge.

PMD (01:25)

Well, thank you for serving the country. The second pressing issue, even before the pandemic, I would say, was the opioid and tobacco crisis in this country, especially in rural parts of America. It's had a devastating impact. I mean, you've seen it firsthand wearing the multiple hats as a physician, and you've also chaired the board of a nonprofit that played a very pioneering in rural America. Could you tell us a little bit about how the FDA is encouraging greater innovation and risk mitigation, and its plans to combat the crisis?

RMC (01:58)

Thanks for bringing us up. It is a huge issue. And I know that you are focused on the social determinants in this meeting that's going on. And I really applaud that because it's so fundamental to both of these issues. And I think and I'm sure everyone in this audience is fully aware that addiction is a growing problem. It's not something that we put behind us. Just announced this month was that over 100,000 Americans died in the last year from drug overdose. And I also want to put out a very important warning that the change in the nature of the supply of high dose Fentanyl and high dose Methamphetamine now is quite substantial – essentially mail-order delivery, right to people's homes with no intermediary as an illicit trade. And we're likely to see a further spike in deaths because it's really a matter of criminal behavior and

is very difficult, something the FDA certainly doesn't control. But in collaboration with the DEA and the national coordinator on Drugs, we've got to come up with a strategy that works. We're going to need the help of the community. But let me just say that we have a list of over 20 specific things that we're going to do related to Opioids at the FDA.

RMC (03:27)

There will be much public discussion about it. I presented at the Opioid summit in Atlanta just about a month ago to begin that list but there are all kinds of things that you might imagine related to prevention: there's acute treatment – you know, we need to get more naloxone out. There ensuring that people have access to evidence-based care if they are undergoing the need for substance use disorder treatment. And then, of course, the social support that's needed because it's not just a matter of medical treatment. Like, everybody knows that the social environment, the joblessness all that's important. But then you got tobacco, and as a cardiologist, I saw a lot of people die in my career from tobacco related illnesses. Before 2015, I sort of thought we had it all under control like we just need to get rid of tobacco, but I learned a lot during my first stint as Commissioner. We're still fighting the battle. Almost 500,000 Americans will die this year from tobacco related illness, so we are pushing through several regulations that we hope will lead to a continued reduction in the use of tobacco products, but also will stem the tide of the vaping epidemic that we're now under. We just got to rule out through the management and budget on a product standard on menthol and tobacco products, and one on cigars. It will be very important in addressing disparities that are occurring in the targeting of particular subpopulations.

But this is a vast battle that we're going to have to continue to fight for a long time coming. And I mentioned nicotine; there will be a lot of discussion about what to do about the levels of nicotine in these products. It's highly addictive.

And then the last point I want to make related to tobacco specifically, we think a lot about this with regard to opioids, that we need an environment for people that socially supportive as they try to become to deal with addiction. It's really severe. I think, as all of you know, with tobacco, if you look at the population currently using tobacco products, you're very aware that people with serious mental illness have very high use. And even among those without serious mental illness, a tremendous rate of living alone, not having good insurance, not having social support. So, we're talking across HHS about a care package. Basically, what is the total environment we need to create, if we actually reach a point where 30 million people are putting aside tobacco products and getting over addiction to nicotine?

PMD (06:26)

Yeah, that's excellent. Thank you for doing that. This particular session that you're speaking at, one of the focuses is artificial intelligence and remote care. And as you know, the pandemic not only has had a huge negative impact on the mental health, but one of the silver linings is that it's sort of brought remote care to the forefront, especially telemedicine and telepsychiatry. But the area of sort of digital apps is still not as mature. There are tens of thousands of mental health apps out there, it's really hard for a consumer to tell

which is a good app, which is a bad app, and only four have actually been cleared by the FDA, to my knowledge, at least to treat specific mental health related disorders. And one of those is for opioid abuse. So, what role do you think digital tools will play in the future of mental health, and how is the FDA looking at this issue?

RMC (07:20)

Well, as she noted at the beginning, I've had a chance to be immersed in this, having worked at Alphabet and spent a lot of time wrestling with the many issues that come up. I would just say to start with, we need to step back and acknowledge that digitization in our society and broad access to the Internet are having profound effects that we don't yet understand. And as we develop technologies with the plasticity that these technologies have, that is as opposed to traditional medical devices, you can change the software very quickly. This is a tremendous potential benefit but also carries very specific risks that we need to be aware of. And I personally believe the assumption that these technologies don't have specific risks is an incorrect assumption. And just like any intervention, the net benefits outweigh the net risk, or they don't, and that determination ultimately will need to be made. But in the meanwhile, like all evolving technologies and areas of innovation, particularly something as expansive as this, where there's such a crossover between a relatively healthy person not dealing with a specific medical problem, and then the things involved when there is a specific medical problem, we got a lot to work out.

So, the FDA is very much adaptive in its approach to regulation. The one thing I would stress more than anything else is that we're looking for systems because let's compare it to a cardiac defibrillator. In my field of Cardiology, when you make a modification to a defibrillator, I think everyone understands you better test it and oftentimes you need to do a complete reassessment of the rest of the benefits. When you make a software modification, that's a whole different thing. It should happen frequently. We want to encourage that, but that means we have to have reliable entities which take seriously their responsibility to ensure that the benefits outweigh the risks and they're not selling things that inadvertently cause problems. And then the last thing to emphasize and I think everybody's aware of this, but I don't think enough, when we use algorithms in health and health care, a small change in the underlying environment or population can make the whole thing go wrong. And so, I give my colleagues at FDA a lot of credit. Not because of me, but they really have emphasized the total product life cycle. When you put an algorithm out there, I think you have an attached responsibility to continuously assess the algorithm, much like post marketing surveillance with drugs and devices, and to adapt it so that it's operating characteristics give you what you need from that algorithm.

PMD (10:16)

That's very well said. In a related question, you're one of the world's leading experts on evidence generation, and I know this is a very important area that you're going to be looking at to see how we can improve the quality of evidence to gain the trust amongst payers, clinicians, and also consumers. Do you want to share some thoughts on what your plans are?

RMC (10:39)

Well, this has been like my whole career, and I feel like the theory of evidence generation keeps getting better and better. The practice, especially in the US, needs a lot of work. Our research system is way too expensive, way too cumbersome. It takes too long. It often doesn't address the questions that really matter to patients and clinicians who care for them. And so, we've got to adapt to, I think, number one, to the interaction of people and technology. The fact that Congress has put the funding out, the whole of the US will have access to high speed Internet. And of course, even people without wealth have cellphones. We will be able to reach 100% of the US population, both for research and for clinical care. And we have to have systems that don't make it so that it takes forever to get something through an IRB. We also have to have systems that identify the important questions and make sure we work together to answer them. One characteristic of the US system that we've talked a lot about -- there are way too many of what Janet Woodcock, my colleague, coined the term SCT, “small crappy trials.”

RMC (12:00)

These are mostly done in academic medical centers by people trying to get tenure or fellows, and they're not going to answer really meaningful questions. And in the meanwhile, since it sucks up all the energy and money and volunteerism, the trials that really matter, the studies that really matter, often don't get done. And we saw this in a major way in COVID, where in the US a lot of people volunteered. Hundreds of thousands of studies were done. In an analysis done by FDA, over 90% couldn't have possibly answered a question that was meaningful to patients. Meanwhile, in the UK, the British health system said it is our job to answer these questions. They simplified the protocols, they did it very inexpensively. They got the key answers to a number of questions that we needed answered. Now, why couldn't a country with our prowess and finances be able to do it? And here I want to particularly pick on you guys in mental health. And as you know, I've done trials in this area, too.

PMD (13:01)

SADHART, for example, the SADHART and the sadhardt CHF.

RMC (13:05)

Sure. I would just say one of the things that we're going to work on a lot; clinicians in the US are under tremendous duress, and your field is probably number one. They're just not enough of you, and you're under constant pressure and financial stress in your systems. We've got to come up with a way to get the evidence that we need. There's a saying which is sort of my motto, “in God we trust, all others must bring high quality evidence.” And it's very much something that, how do we know which interventions are going to work if we don't study them and figure out what's effective and what's not? Focus the limited money and expertise we have on the things that work and stop doing the things that don't work.

PM (13:55)

That's extremely well said. So I'm going to ask you one last question, which is probably one of the most important questions. As I said, the theme of this year's APA is social determinants of health, and you have published several recent papers also on this topic showing the links between socioeconomic disparities and depression and medical comorbidities. Are underserved populations being represented appropriately in drug and device and software and AI trials. What are you seeing from your perspective in terms of increasing diversity and inclusion? And also reducing biases, as you mentioned?

RMC (14:32)

Well, as you know, Murali, this equity is a major focus of the current administration and of HHS and of course, the FDA. The short answer to your question is no. So, we have a lot of work to do. And I think about this in terms of, if you thought about this in terms of a curriculum, we're sort of at the inclusiveness 101 level in this country. I think the NIH, by the way, is doing really well, because at the NIH there's control of the grants and contracts. And if someone's not meeting the plan, they can withhold the money and then things, I think the numbers look pretty good. In the drug and device industry is quite different, as you know, because it's the global industry, only 4% of the world's population is in the US. And of course, if someone developed a product totally outside the US and it had a magnificent benefit, it would be very hard to withhold the product from America. So, there's a much more dynamic tension that we have to deal with. So we're putting out guidances. We're focused on this. It's going to come up in the reviews that we do with industry as protocols are developed.

RMC (15:52)

There's likely to be some laws passed this year. If you watch this carefully, there's some in consideration as we speak that will have more requirements for the medical products industry. But the level 202, I think, is much more complicated because it's not just race, sex, and ethnicity But in addition to that, we have the gender factor now, which is not the same as sex. And we often get these confused and don't really pay the right attention. And we have the dominance of economic and educational disparities particularly affecting rural populations. Yes, the biggest decline in life expectancy in the US right now is in white men who live between West Virginia and Oklahoma. And so we have to expand our definition of inclusivity according to a number of characteristics. But 303 the highest level is something that I think very much relates back to the evidence generation system and it's a global issue. If we believe that populations should be a representative in the United States for products used in the US, what are we saying about the rest of the world when we're only 4% of the world's population?

RMC (17:12)

What would the size of clinical trials need to be to be inclusive of over 250 ethnicities in the world? What are those shared responsibilities? And of course, the reason this is exciting to me because we all know that as data is now in the cloud, there's no reason that globally we couldn't be developing medical products and concepts of clinical care, and sharing the data if we could work out the rules by which we do it. This relates back to one of my priorities. We're hiring at the FDA, I want to make that point. We have

jobs. We're going to be working on these policy issues, but also the implementation together with industry and there's a big focus on global collaboration. We're all dependent on each other. If we didn't believe that before, the pandemic has made that abundantly clear.

PMD (18:06)

But thank you so much for your service! That was really informative, and we hope in the future you'll be able to join the meeting live in person.

RMC (18:13)

I would really look forward to that. Thanks Murali.

PMD (18:16)

Thank you.