John Horigan
All of Us
Oral History

The All of Us Research Program is an ambitious effort to gather health data from one million or more people living in the United States to accelerate research that may improve health. All of Us is working with participants across the country, collecting many types of information over time, and building a database that many researchers can use. This new model could shape how people do research in the future. All of Us will share lessons about what works well with other research programs around the world. The program is supported and overseen by the National Institutes of Health (NIH) and is the result of NIH's Precision Medicine Initiative Working Group of the Advisory Committee to the Director, which concluded its work in 2015.

Condon: Excellent. Okay, I am Aaron Condren, today is Monday, December 11, 2023. I am joined by John Horigan, who is Director of the IRB [Institutional Review Board] and Protocol Compliance and Research Compliance Branch for the All of Us Research Program. Today I'm going to conduct an interview to explore the origin of the All of Us and document it as part of an oral history series for the Office of NIH History and Stetten Museum.

How are you today, John?

Horigan: I'm doing well. Thank you.

Condon: Excellent. To begin with, can you tell me a little bit about your history and what you do?

Horigan: I am part of a field of research ethicists who focus on applied research ethics in the context of human subjects research. Anytime that you engage in research with humans as the subject, and in certain other conditions, like federal funding and various things, it is subject to review by what's called an Institutional Review Board [IRB]. Sometimes it's called a research ethics review board or an ethics committee. That was my entry point to the program very early on. That's the similar role that I've maintained since. I started with the program roughly at its inception, and about the time that the program really formed and started down the pathway of creating a protocol. The NIH formed an external IRB for review of the program, and I was asked to lead those efforts. I did that for around two years, I think it was, and then I took a different job that took me elsewhere, did that for about two years, and then came back in the capacity as the director of the Research Compliance Branch doing the work that I do now.

Condon: Okay, how did you hear about the Precision Medicine Initiative (PMI)?

Horigan: I remember it being born out of some work that the Obama administration was doing. More pertinent at the time to me was the Cancer Moonshot effort that was in tandem with this, as I remember it. At the time, I was doing a lot of work as a contractor for the National Cancer Institute [NCI] running central IRBs for them. The Cancer Moonshot was really the big buzz at the time. At the time, Vice President Biden, I think, if I remember correctly, had lost one of his sons to cancer. There was a whole lot of press around all of this. I think the public in general, but especially people in the research circles, knew that there was this work on a cohort program that was being developed. I had this peripheral knowledge of it, and then eventually, our client at the NCI came to us and said, "Listen"…actually it was even before that …the Office of Science Policy at NIH reached out and said, "Could you support a couple of meetings of this IRB that we're creating?" And we said, "Sure" [and] did that at as a low-cost thing. Facilitated two days' worth of meetings. That was really the beginning of insight into what was being built. Then, I think it was called the PMI cohort or something like that. At the time, it was not yet All of Us. That was really my first entry point. It was, "Hey, we have this IRB for this big cohort we're going to do, we need to do some education around IRB issues and sort of get them up and running." That was sort of the entry point for me.

Condon: Sounds good. I was actually at NCI during the inception of the Moonshot programs.

Horigan: Yeah, they really went in tandem, it felt like.

Condon: Can you expand a little bit more on your role during those early years? You mentioned IRB, can you tell us a little bit more about that?

Horigan: In those early days, the program was starting to do what I'll call research development, some small-ish projects, looking at how they would achieve the larger aim of creating this cohort. Things like asking for feedback on electronic informed consent processes or engaging with different communities to get their feedback about what a program like this should look and feel like. Several of those projects needed some sort of a regulatory analysis to make sure that they're compliant with federal regulations about human subjects research. Many of those things were not deemed to be human subjects research, but the IRB that the NIH had established for this wanted to take a look at those to make those decisions themselves, which is permissible under the rules. It really was done on the up and up. In the earliest days, there was a number of these small sort of let's-get-started projects that came through and we would look at and offer comments on [them]. Most of them under the regulatory structures are probably considered to be exempt human subjects research, meaning they don't need IRB review, but the IRB served that purpose for the program at the time. That was probably the first year [that] we had a lot of those. And in that same time of that first year or so, we did a good amount of work with the program. OSP, the Office of Science Policy, contracted with a company I worked for at the time to

provide full range of support for the IRB. We went from this one-off “Can you facilitate a couple of meetings?” to full support for that IRB, which meant ensuring they had the correct registration with the federal government, making sure there was an FWA [Federal Wide Assurance] in place, various things like this. It was really those early, early foundational sorts of projects.

In that work, we started toward creation of a single protocol. That single protocol was really looking to create the cohort. It was a slew of documents. It was this frantic pace to get everything through. I think eventually the national launch was set for I'll say, May of 2017. It was a mad dash between about December of 2016, right through to May of 2017, to really have everything planned and ready to go. It was a lot of fun for me, because it's a lot of novel approaches to the way informed consent was done and a novel approach to the way participants enroll in research. That was all new and different, and I think in some regard, sort of tech heavy, which was interesting to me, because the program was leaning toward this notion of computers and smartphones, everything is sort of ubiquitous, everybody has them everywhere. Even in geographically remote, or otherwise underserved communities, oftentimes people still have a connection to digital technology through a device. Using devices to be an entry point to research was not brand new, but really, this was the first time I think I saw it done at this scale. That was some of the excitement in those early months.

Condon: Especially when you factor in the mobile technology is bridging the technology gap in rural and underserved communities. What does the term precision medicine mean to you?

Horigan: This is a loaded term for folks in my field. The way I think about it is informed by a lot of conversations we had with the IRB in the early days, and the broad view of what it could mean versus what it means right now. The way that I understand it is this idea that the approach to your health and your wellbeing is tailored to you and informed by you. So whether that's your genetic information, or your health history, really figuring out what will work best for you. I think, to some extent in the care setting, it's also about figuring out what works for you in the non-biological sense, right? If it's something like if you're supposed to give yourself an injection every two days, but you're not comfortable doing that, then it doesn't work for you, right? It's that sort of a thing. But what's interesting is, I think, over time, I started to understand a little bit better the distinction between precision medicine and personalized medicine. To an extent, I think what I just described as more personalized medicine. But when I think of precision medicine, I think about really targeting specific pathways that cause disease or could prevent disease, really tailoring our approaches to care to be informed by the biological consequences of what that does or what that is. I think what I wonder about, I suppose, is whether the public sees that distinction between personalized medicine and precision medicine, and whether they're whether they really ought to be distinct. There's a big philosophical question there that I think we collectively are still wrestling with: What exactly does it mean when we say, “precision medicine” versus “personalized medicine”? I mean, you could say that to some extent all of our health care is personalized, or should be personalized, just by virtue of our interactions with our care providers. What I see precision medicine doing is, rather than taking this a blanket approach like, “We'll just hit everything”, [precision medicine] really targets very specific mechanisms to drive outcomes. Where I saw it most predominantly was in the cancer setting of really targeting pathways

that drive cancer as opposed to just the whole organism, the whole body, really thinking about how we can be precise in the way we deliver care and interventions to do what we're seeking to do.

Condon: Okay, that's actually a very interesting perspective. I don't think I've heard that one yet. The difference between personalized and precision. I think I'd like to explore that outside of this context, because it's an interesting way to look at it. The original name was Precision Medicine Cohort Initiative. That's what it was, and it evolved to the All of Us Research Program. Why did it change? Do you know?

Horigan: It was interesting. We knew it as the cohort program and in fact our federal wide registration, the federal wide assurance registration, I think still uses that term, it hasn't been updated. I think you can't really update it easily. It was interesting to me because we knew that the name of the program might change for the sake of transparency and recruitment purposes. I guess I would say, to some extent, it was sort of, you need a name that's not technical, right? If you're going to deal with the American public, all several 300 million of us, you need to have something that's accessible. I think calling it the Precision Medicine Cohort Initiative is a mouthful, even for someone who does what we do. Calling it the All of Us Research Program, I think spoke to the scope and the intent behind it to be inclusive of everyone and a research program. I've always thought there was a little bit of a missed opportunity in the name in that All of Us. I kind of wish it had been a capital U capital S as in like all of United States or something, but that would have been real gimmicky, I'm sure [All of US]. I'm sure someone in comms [All of Us Division of Communications] out there is groaning knowing that I've just said this. I think what it did when they did switch the name was, I think it made it less technical and more approachable. People could approach it a little bit more readily. When the name change came through, we knew that it would happen, we just didn't know when. We had an inkling of it. I think it did really make it more accessible and something people could relate to a little better.

Condon: What do you think about the name change?

Horigan: I guess a missed opportunity for a different thing there. To me, I think it matters slightly less what you call it, and more what you do with it. I like that it reflects the notion and sort of this value of reflecting the diversity of the United States: the All of Us. It interestingly, the same time, I think it calls out the fact that we, for many years in research have not done a great job of being inclusive. Whether that was exclusion. I mean, for years, I did work where we would see breast cancer studies, where that particular form of breast cancer was the predominant form of breast cancer you'd see in African American women, and yet, we would see awardees basically saying, "Yeah, we expect this to be 60 percent White women in the enrollment and the clinical trials." I always thought that that was problematic for a lot of reasons. But really, what struck me many times was that we sort of as an industry, we hid behind this notion that there was a history with that community. Therefore, Black women were less likely to enroll in a clinical trial because of that history. Yet, at the same time, yes, we can acknowledge that, but it also felt a whole lot like we were just accepting that and saying, "Well, oh well," and not doing anything to change that. When I saw the name, All of Us Research Program, I thought, this is

interesting, because I think it's really a call to shifting the way that we approach research and who's represented in it in a meaningful way. To see where the program has gone over the years, I think that there have been a whole lot of strides made in the right direction. There's still tons and tons and tons to do, but it felt like for the first time, we were paying attention to representation. As an industry as a whole, I think for many, many years and the work that I do, we were very focused on what we call respect for persons, which is this notion that you have decision-making capacity. We asked you to be in research, we disclose to you what the research is about, and you make a choice. I think that there's sort of other principles, things like justice, which has to do with access and representation, all these things and beneficence, you know, doing good through all of this. This was the first time I started to see the folks in my field shift away from this primacy of informed consent and respect for persons; it was like that was where everyone was focused. In fairness, I think that for many, many years, there were certain legal cases and litigation and things like this, and I think, not to disparage attorneys writ large, but I think that many risk management professionals with legal backgrounds pushed very hard on the idea that informed consent was as much about respect for the person as it was protection of the researchers. And this shift toward inclusivity, I think started to move those principles. This notion of respect for persons, beneficence, and justice, it started to rebalance those. It's been interesting to see this emphasis on reference integration for really the first time in my career. It was the first time it was that apparent that it was something people were paying attention to.

Condon: Great. The enrollment of one million participants in 10 years is ambitious. What is being done to reach this goal? When do you expect that to happen?

Horigan: Yeah, what I've seen over the course of the six or seven years I've had some level of involvement with the program is that the number of sites across the country has increased, so the number of health provider organizations has grown. There's been new reach. Recently, there are a couple of institutions that opened enrollment in Puerto Rico, there's a new award out that will cover parts of the central United States that were not covered before. I think there's a lot of attention being paid to that.

The other part of it that I have always thought was interesting is that an individual can enroll from wherever they are, right, in the United States. We're still going to continue to work toward making sure that we are in all the places we can be and all the communities where we can be. I think this year, early this year, I think it may have been in May, we saw some of the first national ad campaigns. There were two ads that ran in People Magazine in May, that were, I think, the first of their kind at that size and scale for the program with that reach. I think we're gonna continue to make those strides. My hope is—we're at 700,000 plus at the moment, so I don't doubt that we're going to reach the million—but my hope is that we're going to do more outreach and figure out new ways to meet people where they are. There are a lot of communities that are medically underserved that are geographically remote [or] technologically maybe not as accessible. I'd like to see us do more work with community organizations to reach those folks. I live in a small community in upstate New York. We don't have a lot of access to health care. There's a couple of good health care systems, which is great, I'm happy we have them. The idea of going to an academic medical center to enroll in a study—it's a two-hour drive to the nearest one. That's one way, so you're talking four hours to drive for the first appointment. It's not likely going to

happen. I'd like to see us really expand that reach, but I'm confident we're going to hit the million. So much so that I just submitted an amendment to the Food and Drug Administration to put the cap at two million instead of one million because I have a feeling that to get the data that we want, we're gonna need to enroll, you know, the size and scale and scope of the data that we want to go share, we'll probably need to enroll well over a million to achieve that. We're well on our way.

Condon: Yeah, working with the understanding that just because someone's enrolled does not mean they're active participants, right?

Horigan: That's right. Yep.

Condon: Great. Another goal of the program, one does not get quite as much billing as the one million participant [goal], is a sharing of data to research institutions. I love this. I actually try to highlight it when I talk to friends and colleagues across the agency. Essentially, this means that the All of Us is providing data for free to research institutions, so they don't have to recruit their own research participants. There's a question in there somewhere. Share with me how this works practically.

Horigan: In the world of human subjects protections, most of the folks who do the kind of work I do around IRB, institutional review boards, ethics review boards, have seen at some point in their career what we call registries and repositories. So, you know, a registry is a register of people with a particular condition. They're oftentimes disease specific. A repository is leftover tissue samples or leftover blood or usually it's a byproduct; sometimes you can collect new specimens with intent to use them. And I often describe our research program to the folks in my field as a very large, unlike any other registry and repository combined because we're pooling healthcare data from folks, electronic health records, and we're pulling in biospecimens, and we're able to do long lead sequence, all of this sort of work. We're putting ourselves in a position to enable research at a scale that I don't think has been done before. To me what it does is at one and the same time, it enables researchers to move quickly toward discoveries that might otherwise take significant time to arrive at—it will still take time, don't get me wrong, but when you think about having a resource like this at your fingertips to go and query that resource, that is much, much easier than starting from ground zero and having to find 1,000 people to recruit and get information on. And the probability of making a discovery, I think, is significantly larger, given the size and scale and scope of the program, right? That we're able to pull together a million Americans, let's hope, who are able to share their records and their biological information and specimens. If there's a million of them, the chances of finding the 1,000 patients across the country who have a particular condition, maybe it's rare, is much higher than if you're just working in your own quadrant of the world, right? To me, that's what really is the power behind this.

At the same time, because of what I do, I tend to think of these things from a risk perspective—risk to the research subject's perspective. I think that what this program does is it distributes that burden of risk to all Americans and not just the Americans who happen to reside in a particular area. We're all sharing in that. But I

think the advantage of that as well, the further advantage, is that we all benefit from it potentially much more. I often when I'm describing this, I use myself as an example. I have a liver condition that really, day to day has little to no impact on me. There's anecdotal evidence that maybe it has a cardioprotective effect, so I like to think that I can eat all the bacon cheeseburgers I want, and I'm not going to die. But you know, we'll find that out. I'll test that. But I imagine that, you know, my practitioner might have maybe 25 of us in an entire caseload. There might be that many, if that many. But that's such a small number that it would be really hard to do any meaningful research with us. If you think about that same group of people in a US-wide [way], in this large scale repository of a million Americans, there might be 2,500 of us, or 25,000 of us, which means that you can do far more meaningful and more powerful research. And it would be paired not only with the health records with various health outcomes, but also with genetic data, so that you could see what are the effects? What do these people have in common? What does this actually play out as? To me, it ends up being a very powerful tool to characterize health prevention, disease treatment, all of these in a really meaningful way.

Condon: Great. Okay, this next one is a little bit sensitive. I understand if you don't want to answer it, but do you have any singular or a favorite research study?

Horigan: One of the most interesting was, and I find this fascinating because I encountered an article on a news outlet's website, about how many steps you take in a day relative to health. And I thought, well, this is interesting. I wear a Fitbit, I have had one for the better part of eight years. And I thought, well, I'm curious, I arbitrarily set a goal of 10,000 steps a day, I have no idea why that's what I chose. Maybe it's what Fitbit recommended, no notion of why. And this particular article talks through recent research findings that said that—I'm gonna summarize this and probably not get it perfectly right—but that about eight [thousand] to 10,000 steps seems to be the range where people either maintained or lost weight, if that was their aim, and that much over 10,000 steps had this diminishing return. If you hit 15,000, or 20,000, it didn't really seem to have much of an effect on weight loss or maintaining. But that somewhere under the 8,000 mark, you know, I think it was probably under 5000, you know, tended to have different health problems. So, weight gain, and those sorts of things seemed more common and less weight loss, if that's what one was aiming for. I remember reading the article and thinking, well, this is cool. Now I know why I have a rationale for setting my target at 10,000 steps that retrospectively, I can apply. But I remember thinking at the time, like, "Who on earth has this data? How did they get this together?" When I started to read through the remainder of the article, I realized that it had been done by researchers at Vanderbilt using the All of Us Research Program. It was the first Fitbit data release; it was the driver project that was done on the back end of that data release. I found myself sending this article to a whole host of family and friends just saying, "This is what we do. This is what this enables." Is it likely to change the face of healthcare? Probably not, but I think it's instructive to thinking about movement and wellbeing; it helps characterize that all the better. I've always sort of pointed to that one as one of interest to me, in large part because I just was reading it and thinking, "This is really cool. How did they do it?" And then realized it was us.

Condon: It's actually impactful because it's changing that automatic step count or automatic target that comes when you get a Fitbit, or I wear a Garmin, when I do it [actively count steps or exercise]. Right? So same type of thing.

In February 2017, All of Us announced that it would issue five million dollars in funding in extramural awards spread over three years. It was entitled All of Us Program Engagement Partners and the funding opportunity number is OT-PM-17-002. From your perspective, what was the impact on how this was received in the healthcare research community?

Horigan: From where I sat, it was an immense opportunity to work directly with community organizations, a big shift from the way that—I'm going to characterize this way larger scale that I probably have any justification for—I think it was one of the first times I saw the NIH shift gears away from awards to academic medical centers and start to work more directly with community organizations. Now, that said, the NIH may have been doing this in other ways, in [other] places before. I know that there's always been room for consumer advocates and patient advocates in the NIH's work. I've experienced that. But this was one of the first times I really saw the NIH shifting into a new zone and saying we want to work with community organizations to promote knowledge about research.

This was the other interesting part: It wasn't all just about All of Us. All of Us was the common thread through all of it, but it was things like increasing healthcare literacy in communities, research literacy and communities. To me, it was this first step in looking at the limitations of the past 75-100 years' worth of research where the government has worked so closely with academic medical centers that have limitations, acknowledging those limitations and saying [that] there are organizations that work in communities who work with people around health care, around research, around advancing science, and we need to be engaging them in the conversation. I think it was a breath of fresh air in a way. I remember having a couple of conversations with the then IRB chair and the co-chair, about this being the right approach for a program like this to take to really put its money where its mouth is and really recognize and respect the value of diversity in the United States and engage with those groups to talk with them and see what matters and share what we're doing. To me, it was groundbreaking in the sense that the NIH was really shifting gears in a meaningful way. But to the extent that that had been done elsewhere, I don't know. It was a very visible shift to me.

Condon: Great, it was clear to me in my work within the program, as well as to my review of the historical material, that inclusivity has always been paramount in both the enrollment of participants and in the workforce composition of the All of Us research program. Why is it important that participants be from diverse ethnicities or socioeconomic backgrounds?

Horigan: Oh, man. The easy answer is that if you're not represented, you're not represented, right, and I realized that's a circular statement. But the work that the program has done for representation is important because so many people have been excluded from research in the past. By design, in many cases, and sometimes by

arbitrary rationales. For many years, there was a running joke in the community of research ethicists that I work in about researchers who wanted to exclude women from even psychosocial studies, things like psychological survey data, they didn't want women to participate. The rationale given was well, because of hormonal fluctuations in the course of a given month, a woman's behavior could modulate widely, and which is just utterly ridiculous. It just sort of ignores the lived experience of half of the population off the bat. And you would see things like, “Oh, well, those people are hard to reach. I don't want to put the effort in” No one said they didn't want to put the effort in, but that was the apparent paradigm. To me, taking the steps to ensure representation is tantamount to saying to all those communities, we know you're here, and we want to invite you to be part of what we're doing. We're not going to exclude people anymore.

And you know, certainly there are research studies where it makes sense to limit participation. If you're studying disease of a particular organ that one group of people doesn't have, then fine. It makes sense not to include those people. But the inclusivity can look different. It can be rather than saying we're doing a study of women because we're studying uterine cancer or something like this. Well, to say women is also limiting. So to say we're studying people who have a uterus, right, and who have of uterine cancer. That can be trans men, that can be people who identify differently. So I think this program has done a lot for shifting, kind of moving, the dial in that space to be respectful of the fact that there are participants with many different lived experiences, to think about how those experiences might affect their health and wellbeing. I sit here as a White guy. I'm gay. I'm a White man. I live in a small community in rural New York state. My access to care is largely unaffected by that, more affected by my geography, but in other places, the same sort of characteristics, the lived experience can be widely different, just because of who someone is. We know through research studies that practitioners generally rate the ranking of pain for African American patients as lower. There's a presumption hiding in there that's not supported by data. We know that women, oftentimes, especially around maternal healthcare, obstetrics and gynecology work, there's under-representation and research in that space, it's just not done. To think of it as an opportunity to really throw the doors open and bring people in and make research work for everyone is really heartening to me. It's important in the long run, though, that the database that we're creating, this resource that we're creating, actually be usable. And I think the way you do that is through as diverse a cohort as possible.

Condon: From your perspective, what are the ways we're the steps we are engaging in to assure that we have a diverse cohort?

Horigan: I think a big part of it, this idea of working with communities to drive interest in research in the program, I think that's been a big part of it. What I've seen in an interesting way is our IRB sort of holding the program's feet to the fire. The program is doing, in earnest, is doing good work toward the end of really having a diverse cohort. The IRB is also particularly concerned about making sure that when we say participation is open to everyone; they want us to demonstrate that. I'll give an example that came through some conversations a year and a half ago, or maybe about two years ago, with the IRB where we said, okay, participation is open to all. The reviewer said, “Great, we would like to see some numbers around that.” We gave them demographic numbers, and we focused on race, ethnicity, socio demographic data, all these different things. The IRB came

back and asked, “Okay, what about disability status?” Because it's one thing to say you're open to everybody and then through systematic barriers, not represent a population. Then to crunch the numbers and figure out what could we show them? So it’s this interesting interaction where the IRB said, “Okay, show us where the rubber meets the road here, and really tell us, show us that you're doing what you say you're doing.” From my perspective, it's a really interesting sort of accountability that we say we're going to do it and the program does work in that direction through communities through all of this work. We have this external IRB that says to us, prove it, prove that you're doing what you're saying you're doing. Just hand waving isn't gonna work, in this case, we want you to show us the data. Certainly, we will always still have work to do in that space. It's just always going to have to be done, but I think the focus this program has put on it is unique.

Condon: I agree with you. Privacy is always a concern when gathering and storing study participant health data. From your perspective, what are the main ethical challenges you see with collecting, storing, and reporting that data to participants?

Horigan: It's multifaceted. I think if you ask someone to share their electronic health records, it can feel invasive in the sense that it's some of our deepest, most private information. It's so deeply about me and who I am, and my experience in the world, that I think it just comes with an inherent sense of risk; people are protective of it. Where I think the program does particularly well is communicating to participants how we're going to de-identify that data so it can be used for research purposes. And having protections in place even with those provisions for de-identification in place, having protections against stigmatizing research, and sort of monitoring through the RAB—I'm going to call it the resource access board, but I don't know if that's still what the acronym stands for—to really keep an eye on what's being done on the researcher workbench.

But what I see is a really interesting approach to this, is a lot of caution about the data we release in conjunction, right. One data point by itself may not be identifiable. But when you pair it with three or four others that are also in the system, you might be able to figure out oh, that's John, and he's over here. But I think we've been very thoughtful about that. Recently, there's been a shift to reveal a greater level of detail for race and ethnicity data in the database, in the researcher facing database. We went through some effort to make sure that that wasn't going to increase the likelihood of re-identification of a participant, and we went to the IRB and said, “This is our plan. This is what we're going to do. Do you have ethical concerns beyond what we're talking about?” The IRB kind of came back and said, “Yep, no, you've done a good job. We agree, that's fine to proceed.” I think, in the big picture, the privacy concern will probably be something that some individuals decide not to participate on that basis, that they want to protect their privacy. And I think as a program, it's incumbent on us to recognize that, and respect it, and not pressure people.

Condon: From the beginning of the Precision Medicine Initiative, All of Us was meant to be different. In what ways has that been true? How is it different from other research efforts in the past, or even other research happening now? And you've hit that a little bit throughout our discussion. If you can expand a bit.

Horigan: To me, the biggest thing that stands out as I think about the program and how it's different is the emphasis on inclusion and the scale. The scale is sort of a novelty in some way, right, to have a million Americans' data in one place like that. That's just sort of a promise of what you could do with that. But to think about in any meaningful way how are we different—there are tons of registries and repositories and projects like this out there. They tend to be smaller in terms of number of participants, but also in terms of their reach, they may not have this broad-based approach to sharing that we do. To me, it's sort of twofold. It's this part of inclusivity, and then broad sharing. The intent is there to make sure that the data that we're collecting can be used as broadly as possible, which I think enables a whole host of researchers out there to access this data and do the research they want to do. That is one facet of it.

The other is the inclusivity. I don't think I have seen other research programs go as far as this program has to make sure that there's representation. It can feel funny, I think, to talk about representation like underrepresented in biomedical research and representative biomedical research, sometimes in the way that we do, it feels almost as if I think many of us came up in an era where we were supposed to be agnostic to so many things like race, like ethnicity. I think that realization has dawned on many of us that that agnosticism doesn't work; it becomes too easy to fall into habits and patterns and have implicit biases or latent biases show up in the way we do things. While at times it feels awkward, I think that's because of our past experiences. What's really refreshing about it is that everyone is talking about it. It's not just one person with a bullhorn over here saying, hey, we need to be inclusive. It's at every layer of the program, since the beginning.

So, just last week, I was attending a conference. It was the Public Responsibility in Medicine and Research Conference, which is the Animal Care and Use Committee and also the Human Subjects Protection community that I work in. It struck me my job is very luxurious in the sense that this program was established with values from the beginning that we work very hard to live up to. I think many other institutions out there, other research programs out there, have mission statements, vision statements, value statements, and they have to recenter periodically around those. I think because this program had that from the very beginning, we've been able to really weave that into everything we do. As a result of that, inclusivity has been a major part of what we do. I see it in the workforce, I see it in the representation in the database, I think we're seeing it in the access to the resources, who the researchers are who are accessing the data, really thinking about how that plays out all the way through from collection to utilization of the data. I think is something very unique about this program that I hope will change the way that research gets done going forward.

Condon: Even with the best of intentions, sometimes the mark is missed, right? Can you identify any missed opportunities for us being as different as we could be?

Horigan: I think the one that stands out to me, Aaron, is sort of an obvious one in the first couple of years after the initial launch, which was engaging with the AIAN [American Indian Alaska Native] community. I have to acknowledge here I approach research ethics from a heavily Western influenced perspective. We sort of operate in this world where these three moral principles guide everything we do: respect for persons, beneficence, and

justice. That notion of “respect for persons” really centers the person as an individual. Where I think the AIAN community is different from that is that, yes, individuals can make decisions for themselves about any number of things, but there is a communal responsibility and a communal decision-making that happens in those communities. I struggled with that, myself, I think because it is not something I'm familiar with. The notion that somebody could restrict my ability to make the choices I want to make does not sit well with me. I recognize that that's a bias I have. And I think in those early days of the program, we were operating so much from that sort of Western-informed perspective on biomedical research, that we made some missteps with the AIAN community. What was really telling to me was not so much that we made the missteps like that; that's almost to be expected given the world we were in at that point. But I think the ownership the program took of that mistake and very publicly saying, “This was a mistake on our part. We should have engaged with the community before we did this and really put some effort into repairing those relationships and really building those relationships.” It was one of those moments where, I think it was in 2017 or 2018, I can't remember exactly now, but there was a lot of work done by the program to say, we did this wrong, and we will fix it. There's a whole group within the Division of Engagement now [that was] originally under the COO’s [Chief Operating Officer’s] office, working with the AIAN community in earnest to make sure that we're holding up our end of the bargain; we want to include those communities in research, but we need to do that with respect to their community values. And even though folks like me sitting in my job think on a personal basis, like I bristle at some of those ideas, they're not mine. It's not for me to say, and so having respect for that sort of communal autonomy matters just as much. So that, to me, has been a learning experience professionally and personally. But it's also, I think, a learning experience for the program to have made that misstep, really be called out on it and say, publicly, we made a mistake, and we're going to act to correct this. That's probably the most obvious instance I can think of where we've made a mistake, and it's one that I think has big ramifications for trust in the community. I think we've learned a great deal from it.

Condon: Yeah, there's a great deal of mistrust with that community in particular [regarding] treatment and research in this country. I think it's important [to acknowledge]. So great, thank you for that.

The program being different meant that there was a lot of work to create something from the ground up. What are some of the unique challenges of creating something that is intentionally different from research that came before?

Horigan: Oh, man, this is a good one. I will say, and this can live on in the record, that there's a little bit of building the plane while we're flying it at times, and that is exciting, enthralling, scary, dangerous, all of the things you imagine it would be, it is. But I think what that does is it creates a sense of not urgency, but importance to the work that we're doing. That we need to get it done and we need to get it done right. And so, there's a great deal of intent that goes into it. Tell you what, ask me that question again, I want to make sure I'm hitting this right.

Condon: Being different meant that there was a lot of work to create something from the ground up. What are some of the unique challenges of creating something that is intentionally different from research that came before it?

Horigan: One of the things that has been apparent to me in my role is that, oftentimes, this program is pushing boundaries. And moving into spaces where the IRB, the regulated research world hasn't gone before. In the last probably three or four years, there's been a whole lot of discussion about what they call decentralized clinical trials. I've always kind of rolled my eyes at it, thinking, okay, great, that's not that big a deal, but because of the COVID-19 pandemic, there was this shift to try to figure out how you could have people enrolled in clinical trials and self-report certain data points using apps, using mobile whatever it could be. I remember thinking in 2020, we've been doing this for a while now, but, as I reflect on that part of what was interesting, is this program was different. It was meant to allow people to join the program from their couch, from wherever they were. That's created a need to look at what the program is proposing through a slightly different lens as a regulator.

Normally, for example, let's say you go to one of our health provider organizations to enroll in the program, one of the first things that happens is that you go through the consent process, the informed consent process. Eventually you would consent to participation if that's what you chose, or you would say, I'm not interested, thank you so much, and you decline. Within that space, [there is] such a novelty in that space within this program in terms of how you participate; yes to this, no to this, yes to this other thing. There's a lot of options that respect participant choice. That's not so much novel as it is just complicating, right? There's a lot of complications to that. But what was novel to me was that through a regulator's lens, we look at that and say, "Okay, who is obtaining consent?" "Who is ushering you through the consent process?" "Who is answering your questions?", and we think usually frontline research staff would be those folks. We think of them as being engaged in the research; they are doing the research. The flip side of that is if I pull up the consent form in an app, online, at home, there is no person with whom I'm interacting as part of the consent process. I'm interacting with a video online; I'm answering quiz questions. I can email my questions or even call the support center and get questions answered. But there's no person who is engaged in the research seeing me through as a participant in those steps. That was to me sort of groundbreaking—it happens in other places, online surveys, mailed surveys, that sort of thing, but this was really unique and a different way of thinking about things.

It periodically bubbles up as a weird quirk of our program, but it does mean that there are times when we have to explain things differently. What it would mean for my office in particular, is that there are times when there is something that looks irregular in the way we do research because nobody actually, quote unquote, no person obtained the consent of those individuals, they consented in their own right. We have a tool that we call our note to file, which is a note to our records, that explains a particular circumstance, because we know that it'll look funny in the history of the program…that, 15 years from now, if we're still around doing this, that's a little too early for me to be retired, but maybe, 15 years from now, I'm not going to remember what I did today. And so, if I have a note of explanation that says this thing looks funny, and here's why, you know, it's okay. That's been a really useful tool for us.

But you're right that in doing this, it has been different that the tech heavy nature of it has been different [because of] the way in which the data moves from one location to the DRC [All of Us Data Research Center], etc., and then out to the public for use on the researcher workbench. Those are all novel. It has required on many occasions us taking a step back and looking at the way IRBs think about this sort of content and retooling that a little bit. Another example is recruitment. The online mechanisms at this point in 2023, it's not that novel, but in 2018, when we were looking at some of this thinking about how you use what are called UTMs, urgent tracking modules or something of that nature, how do you use those to recruit people and figure out whether your advertising works? Does it draw on the people you intend to draw and who does it draw? That has been an interesting space to continue to grow into and I think we're getting as a field, not just our program, I think everybody's getting a little bit more sophisticated in that space. There's the part where sometimes we look to the federal government regulators for guidance to say, “How do we apply your regulations to what we're doing over here?” I've not hit a full on stop on any of that yet. We've had to look at guidance from regulators and even seek advice from regulators to say, “How do we approach this, because what we're doing is different.” But they've been welcomed challenges, all of them, in an interesting, intellectually stimulating way for doing this work. It's not just a great big registry repository; it always comes with something new and different.

Hopefully, we're paving the way that will change a lot of different types of industries that the government is involved with. I, for one, think it's a wonderful way forward. It seems like we're really opening it up for communities with full access to a diverse, very diverse group of people and diverse participants.

Condon: That concludes my list of questions for you, John, do you have anything else you'd like to share before we go off record?

Horigan: No, I think that this was great. This is a lot of fun. It's fun to reflect on this.

Condon: All right, great. Thank you very much for your time today.