Dr. Josh Denny
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 : I'm Aaron Condon. and it is Wednesday, October 11, 2023. I'm joined by Dr. Josh Denny, the current CEO of the All of Us Research Program. Today I'm going to conduct an interview to explore the origin of All of Us and document it as part of an oral history series with the Office of NIH History and Stetten Museum. Josh, how are you?

Denny: I'm great, Aaron. It's a pleasure to be with you.

Condon: It's a pleasure to see you as well. Thank you for talking to me today. Okay. Josh, how did you learn about the Precision Medicine effort, and how did you become part of it?

Denny: Wow. I guess my first recollection, the first contact, was in late 2014, mid to late 2014, when my former boss, who had left Vanderbilt, sent me an email to ask if I wanted to be on something that was kind of hush hush around what we could do that would further the kind of precision medicine efforts we had begun at Vanderbilt, but that we could do at a potentially bigger scale. At the time, he was independently working with the NIH as one of a couple of people helping think through what the next vision could be. He recruited me basically to write a position paper around what this could look like and how we could do things. There were four position papers written that detailed potential opportunities for precision medicine at a national scale, and how we might do things. That's how I got involved from the beginning, and it was fun working on something revolutionary. I guess most of it, I think, was written in November, December. Thinking through some of the opportunities, we came up with some creative ideas, which became part of what we did for All of Us.

Condon: Okay, and who was your boss at that time?

Denny: Well, my actual boss was very different. Dan Masys [Daniel Masys, MD, University of Washington] was the guy I was working with. He was my original department chair at Vanderbilt who hired me. He left Vanderbilt several years before that to basically kind of retire, but he was the most active retired guy I knew for years. He was doing the kind of projects that he wanted to do that were cool, and this was one of them. He ended up working as a, gosh, I forget what the term is, but maybe he was an IPA [Intergovernmental Personnel Act temporary employee]. But he worked with the NIH during that 2015 time, when we wrote the ACD [NIH Advisory Committee to the Director] working group report. We got to work very closely together, at that time point, writing the ACD working group report.

Condon: Okay, so yeah, thanks a lot for mentioning the working group report, because that was a big foundational document for the organization. Let's explore that a little bit further. Can you describe your role during the inception of the program but also during your period with the working group?

Denny: In January in the State of the Union [address], President Obama announced the Precision Medicine Initiative (PMI). Those of us who had been part of those teams had been getting emails that [stated] "hey," almost daily, "There might be an announcement; there might not be an announcement at the State of Union." Obviously, Francis [Francis Collins, then NIH Director] will tell you that detailed part of the story. There was an announcement, and then on January 30, there was a much more detailed announcement of the Precision Medicine Initiative, and what this could look like. We watched that and it was exciting. Soon thereafter, I remember an email coming to invite me to be part of the ACD working group for this project. There was a process in between a big workshop that happened in February, which I was part of, and delivered a vision for amongst several other people. I remember when I got that email, I was coming home from another trip to [Washington] D.C., and I was waiting for my commuter flight and multitasking as I always do. I missed my plane because of that email. As a fun story and seeing that and replying, I missed the call for my shuttle bus and had to get another flight home. So yes, I was ecstatic about being part of that. That crew kicked off; we wrote our report and finished, I think, in September of 2015. I became an IPA to the NIH and worked as a senior adviser to the NIH Director, Francis. My primary job was to really help, be an advisor, writer, person in residence, to help make sure this working group process came to be and we wrote our report. I did a lot of the research to help the working group come up with what it would do—vision cast and those kinds of things.

I was an in-house person and devoted a lot of my time to writing that and putting together, with several other people here [including] Gwen Jenkins and Kathy Hudson, of course, and Francis was involved, of course, and Dan Masys, my prior Vanderbilt boss helped as well. Then other people from the working group ended up writing sections, as well. That was an exciting time. During that time, putting that together. So many ideas. We knew we wanted to get to a million [participants], but how do we build that cohort? There's lots of stories I could talk about how we got through to what we came to. Whether

it would be a fresh cohort, would be a cohort of cohorts, would we be like Framingham on steroids? What the population mix would be like. We eventually came to the idea that it needed to be a fresh cohort. We wanted to do things new, we wanted to really focus on diversity. We really wanted to focus on using things like electronic health records [EHRs] and centralization of data. These are really core decisions that were hotly contested at the early debates about what we wanted to do in the program. I think that we have found that a lot of these things that we thought were very pie in the sky at the time had become, I don't want to say they're easier to do than we thought they would be, but we did a lot of things that a lot of people in the working group thought were not possible when we wrote the blueprint for this. And some of them have been—I'm glad we made those decisions—and they have become a pattern that's been more what would be expected maybe. I shouldn't say that's easy, but looking back, I can't imagine doing it a different way. Can you imagine if we didn't have a focus on diversity, if we didn't collect and centralize a bunch of EHRs? I think that would have really looked wrong. From the current perspective, and how we're able to get people to the data and let them do research, as opposed to the typical process of the time of downloading data from all sorts of places or having a typical research population that was non-diverse. It really would have been ignoring what were clear, I think, signs at the time, and have clearly been the right choice of where we stand now.

Condon: That's wonderful. Those are cornerstones of the program that are, well, I think, what draws most people to their program today. It is a great thing. What does precision medicine mean to you?

Denny: There's evolution of these terms, individualized medicine, personalized medicine, precision medicine. What precision medicine brings uniquely to the table is the idea that we can get better at science, that we can think about medicine in a way that's more not just individualized to you, but more precise to you. That means that we're doing things hopefully better with the right treatment at the right time, without side effects, and to target the exact condition that you have. And to get smarter, not just thinking about the individual may have diabetes, but they have diabetes, and they also have kidney failure, and maybe they have not just type two diabetes, but maybe there's a subtype of type two diabetes that we later define, and we think about the core morbidities. We think about what's really driving it and what medications are they most likely to respond to. That's about disease treatment. But then the other part is, can we get to the disease before it's symptomatic? Can we get to prevention in a way that isn't just one size fits all, but it's more tailored to the individual, and what their risks? Part of [the risks are] genetic, part of which is environment, part of which is lifestyle, and really thinking about that holistically. It's personalized medicine that really gets at a more accurate understanding of what's going on to better treat and preemptively, maybe, avoid the need to treat where we can, for a health journey that's going to lead to better health for the individual. And, of course, in our thought for all populations, to really make sure that we're addressing precision medicine in an equitable way.

Condon: Okay, great. So, you mentioned, one million participants, that's one of our big goals. Another goal of the program is one that doesn't get quite as much as attention as a one million participant goal is

the sharing of data to research institutions. I love this. I've been at NIH for a very long time, so I know a little bit about how it works, to have to recruit participants and the cost and the time and the effort and resources that are involved in that. The fact that we give our data for free to researchers across the nation is amazing. My question about that is, how did the data sharing element begin, and what models, commitments, or concerns led to including it in the All of Us design?

Denny: This is an area that's exciting to me [because] we have beaten our goals for what could be done to centralize data and make it available to as many researchers as possible. We beat our ACD working group goals and we're beating our estimates for where we want to be in 2026 that we established a couple of years ago. To do that, you must pull the data together, you must convince everyone that's contributing. The hard part is not the participants, it's the institutions that have data, and bring them together. Then, put them in one place, harmonize them, and then create an infrastructure and make them available to as many research institutions as possible, in a way that is safe, secure, protects privacy. In the work that we did at Vanderbilt, prior to me coming here, prior to All of Us existing, we created a research database, where patients at Vanderbilt could decide to become participants in this research study in a way that was fully de-identified. That has a drawback—we couldn't recontact them if we found something—but it also taught us how to do this in a way that really could protect privacy. It taught me, I guess, and the other people that worked in the program, [to answer the question] how do you really protect privacy? It is hard to figure out how to do this. We figured out how to do it computationally. We learned a lot that powered that. But we also learned that we could pull together electronic health information from one site, but then we tried to combine it against other sites. It took lots of people and years of time to do it.

That's just one study, and then how do you turn that crank off [to acknowledge] all the great hypotheses that researchers have? Then how do you share it with people so you can get other researchers doing it? From the beginning, we knew All of Us had to be different. We had to really be transformative, and to really accelerate science and health discovery. And those breakthroughs, we had to figure out how do we get that information into as many researchers' hands as possible in a way that really facilitated their ability to do science. We wanted to centralize the data, not force people to have to ask for it and fill out forms across each institution, and then maybe fight to release the data. We wanted to bring it together, harmonize it, and then control it to allow proof researchers to access it. Then we made the decision that we wanted them to do it in our cloud, our protected cloud, and create the resources for them to do it because it would make it safer and more secure. It would allow us to control and monitor access, and more quickly respond if there's a problem in the process. We believe we've been really democratized in who's able to get access. The person from a high resourced, classic R01 institution has the same computing abilities, essentially, as someone that's coming from a low research institution, or community college. Imagine, a high school student can come in and get the same computing facilities to do incredibly complicated analyses as someone who could have great resources at their local institution. That means more people get to ask questions; we help build the biomedical resource workforce in a way that maybe we haven't before. I think that ultimately it is going to lead to more science being done faster in a secure way and to create better outcomes for everybody.

Condon: I think it’s going to be great innovation just because of that alone. We only have a few minutes, so I'm going to skip down to privacy, which is, as you mentioned, always a concern, especially when gathering and storing participant health data. What are the main ethical considerations of health care providers having access to data that could be considered clinically actionable when providing treatment for unrelated matters?

Denny: I think one of the things we found early on in this project is that our participants, when we talked to them in what we call our engagement studios [for] individual participants or potential participants, they wanted to have control over their health information. We return information to our participants of new discoveries first and let them be the person who takes it to their physician, if they want to, and we help that process. So, returning value, returning information to participants is something we also wanted to be a pioneer in. I think we've done that [by] returning genetic information, health information, we're going to keep expanding that. In some cases, participants can see the electronic health information that we're capturing. We'd like to make that more transparent as well, over time, so we're working on all these problems. And as we go forward with more lab tests and stuff, we'll do the same thing. That's part of that avenue. As we generate information about a participant, they're the first ones to know, we're going to support that decision if they decide to take it to the provider and see how it alters care. We'll help them get a clinical test, where we can as well, if it's a research test that we have.

Additionally, the data we must keep secure; we must protect its privacy, we must protect its security. That's really job one, because if you don't have trust from your participants, not just in how you store the data, but how you're going to be transparent about protecting it, if there ever is a breach, letting them know and communicating with them. Certainly, doing everything you can do to be best in class, to secure your data and protect it in all the ways possible, that we can protect it and test it continuously. We must do that, to maintain that trust. Because it's a longitudinal journey with our participants, we want them to stay with us for decades. That will be the real power of understanding exposure, that maybe you have an environmental exposure decades ago, it may take a long time to develop the risk for cancer or develop heart disease or things like that. Those will be the ways we learn those kinds of knowledge. To do that, we must have trust. So, science moves at the speed of trust. We must protect privacy, security, and that comes through the whole aspect of research to how we return results and let them use [the information] to change their healthcare.

Condon: Great. As a quick follow up to that, how should health care providers address inconsistencies in medical histories and data provided by the All of Us, especially concerning potentially sensitive personal issues?

Denny: You mean, a provider seeing a patient that has an All of Us result?

Condon: If they, by any chance, have data from All of Us, and then have data from their own records, or the electronic health record that is not in All of Us data or there's a discrepancy. How should providers address that?

Denny: Okay, so if you are a patient presenting to a provider, I think that's going to have to be a process of going through and really talking with the patient and working through it. There could be follow up clinical tests. For the most part, we're not going to have clinical information that their provider doesn't have, but what we could have is genomic information that the provider doesn't have, and so that's new information that could change their risk profile, screening recommendations, things like that. Now, we do know that within medical records, there can be discrepancies in some; there can be errors. Some of that's just very natural. I think a patient has—I was provider, as you probably know, for 17 years before moving here—and so, I think the patient has condition X and over time, I realize it's condition Y. This is very common because a lot of times, it takes some time to figure out which of the class of conditions that someone may have; some autoimmune conditions, for example, one condition morphs to another. Those aren't really discrepancies, but they can look like discrepancies when you do an analysis, and you must figure out how to do that. We try to provide tools for the research analysis perspective, to let researchers see the course of one's history and build algorithms to kind of figure out what's going on there. Over time, we might find ways to leverage the participants as well to show them things that may look like discrepancies, [such as asking] “Did you rely on these medications? Yes or no.” Maybe there's an opportunity to say, “This medication didn't work for me, and I had this side effect.” Maybe it looks like we have from two different places, differences of conditions? Did you look through this, and give us some feedback on your heart disease, or Crohn's or whatever the condition might be, and an opportunity for participants to tell us about their medical condition. I think that that's a real opportunity for us to have that interaction with participants that will benefit research as well.

Condon: Great. Josh, that concludes my list of questions for today. You have anything you want to add before we stop?

Denny: I'll just say it's a real pleasure to talk with you and tell some of this story. Since day one hearing about this project, I have been so energized by the potential to do things in this program that are unlike anything else I've worked on. That's why when the opportunity came to join the NIH, I wanted to do it, there's just such opportunity to make a real difference in people's lives. As a provider for 17 years, as a father and son, and all the different relationships I have, you just see real opportunities where we don't know enough as doctors. There's a difference we could provide. I've seen dramatic changes already in my life through research studies like this. I'm really excited about the change we can make that will make real differences to the lives of our participants and the lives of people in the world. That's why I'm

here. I'm just so excited about where we are, and so that's what I'll leave with is the future is just amazingly bright.

Condon: It sounds great. Excellent, Josh, thanks a lot.