Transcript of the **August 2022 “ASCI Perspectives” video**

*Interview with Valerie A. Arboleda, MD, PhD, UCLA (elected 2022)*

*Interviewed by Patrick Nana-Sinkam, MD, Virginia Commonwealth University (elected 2019)*

Note: The text has been edited for readability by ASCI staff.

**Dr. Patrick Nana-Sinkam:** Good afternoon, and welcome to ASCI Perspectives. My name is Patrick Nana-Sinkam, and today I have the pleasure of introducing Dr. Valerie Arboleda. Dr. Arboleda is Assistant Professor of Pathology, Laboratory Medicine, and Human Genetics at the University of California, Los Angeles. Dr. Arboleda has been very successful in a relatively short career, having been awarded the NIH Director’s Early Independence Award and several other NIH awards as well as fellowships. The Arboleta laboratory is focused on applying genomic tools and large data sets to understanding how both rare and common human genetic variations lead to human disease. Dr. Arboleda, welcome and congratulations on your recent election to the ASCI.

**Dr. Valerie A. Arboleda:** Thank you very much. I’m honored to be a part of the ASCI community.

**PNS:** Dr. Arboleda, I’d like to ask you as a starting question to share with us a bit about your career path, and in particular your background and what attracted you to this path as a physician-scientist.

**VAA:** I’ve been thinking about that a little bit more recently as I’m mentoring students. It’s not something that I think there was an active decision. It kind of fell into place, and I think a lot of things aligned to help me make that decision, to help that decision be easy. I personally come from a long line of health professionals. I have a lot of relatives . . . So, I’m Filipino, and my parents, they’re both physicians, they work in primary care. They immigrated here from the Philippines just before I was born, and that immigrant community sort of lifestyle — they were physicians; I have a lot of family nurses, physical therapists, working as CNAs [certified nursing assistants] all over the health professional community. And the focus when I was growing up was really around: find a good, stable job. I did not know a lot of scientists. I would say that I went to college, that was the first time I really sort of said, “Well, what do I need to do to go to med school?” And people had told me, “You should go and join a research lab,” and so that's what I went and did. And that was my first introduction to science.

And I stayed in the lab for four years, and it was not to check a box on the CV, but it was because I really, really enjoyed it. And at the end of that four years of training, I thought to myself, “Well, I could do an MD-PhD. I don’t really know what that path looks like, that’s a really long road.” And so I applied as an MD . . . I don’t want to say MD-only, because that makes it sound like it’s “just” an MD, but I applied as an MD, and I ended up at UCLA. I had in the back of my head thought, “Well, if I have a chance to do a little bit more research, let's explore that a little bit more.” And so when I saw this HHMI [Howard Hughes Medical Institute] Medical Fellows Scholars — it’s a program where you can take a year out between your second
year and third year of med school, or between your third and fourth year — I did that and I kind of just fell in love with research. I didn’t want to go back to med school, and so when I spoke with the program directors of our MSTP [Medical Scientist Training Program], they had me do a formal application. I did the interview process, and they said, “Well, we’ll take you.” That sort of started me down a path, and I never really looked back at that point.

I did finish my PhD, I finished my MD, and then when that decision point came to do a residency, I think it was just — it was another decision tree for me: Do I want to see patients? Do I want to do more research? And that was a much harder decision, because when I went into med school — when many of us go into med school — you go in because you want to help people and you want to see patients, and that was a very hard thing for me to give up. But in the end, I realized if I had to make a choice and just do one, I really wanted to have a research career. And so I ended up doing pathology and lab medicine because I couldn’t quite let go of the clinical aspect. And that was a really fun residency, because it is a lot more . . . I won’t say research-oriented, but you do learn a lot more about the ins and outs and how the black box of a diagnostic testing works. It’s almost like being in a research lab in some ways. Once I was in laboratory medicine, I think, I was doing research, I was helping out building new tests, and that kind of got me. And I fell in love with both genetics and testing, and those two things just . . . those jibed. I had done my PhD in human genetics and looking at rare diseases, I could do genetic testing, and it all fell into place, and that’s why I’m still here, because it was an amazing research experience.

I had really supportive mentors all throughout my training: people who I knew really well and people who I met along the way, including some faculty who I now know are part of ASCI, who told me, “It’s a long road, so take your time and do it the way you want to do it. And don’t let people push you down and tell you that it’s not worth it, because it’s a really fun career.” And at the end, when you’re able to run a research program and mentor students, I’m kind of on that other end looking back and thinking, “Wow, this is really fun, and I really enjoy all parts of my job” — less so the bureaucratic pieces — but all of the parts where I’m working with students and we’re doing new discoveries and being the first people to see certain types of data. It’s been really fun.

PNS: I want to ask you a little bit about that, that path that you’ve taken. You’re at this really, I think, unique intersection between genetic testing and clinical medicine, and I know that your laboratory has really been focused on: How do you go about integrating these large data sets, and how do you make sense of them? Which is really something that those of us who are novices struggle with. We don’t have a lot of understanding, so you’re really an emerging expert in this area. I want to ask you about this in the context of
the COVID pandemic. I think there’s so many things that we’ve learned about the COVID pandemic: it’s highlighted the inequities that exist in health care, broadly speaking. It’s also highlighted the importance of rapid drug development and the fact that we can, if we mobilize all of our forces, develop drugs relatively quickly if we’re all focused in. And it’s also highlighted some of the shortcomings that exist in point-of-care testing, and how do we get widespread testing to broad communities, particularly communities that sometimes don’t necessarily have access to that testing? How do we do it in an efficient way, in a specific and a sensitive way, when we think about diagnostic testing?

So with all of that in context, can you share with us some of the work that you’ve done, really in collaboration with many colleagues, in trying to address this issue of the testing in COVID? I know that you worked on something known as SwabSeq, and you’ve published some papers in that space. Could you share with the audience how that came about and where you see that work going?

**VAA:** Yes. SwabSeq was sort of a really fun . . . I’ll call it a detour. As a resident when I was in training, one of my favorite rotations was actually with our infectious disease group. I worked closely with Omai Garner, who’s now our Director of Clinical Microbiology. And when I started my research lab, I kind of moved away from infectious disease because I’m not trained in infectious disease or in microbiology. But I am trained in genetics, so when the pandemic started, there was a number of my colleagues from both human genetics and computational medicine who said, “This is sort of strange, we’re a genetics department, this is qRT-PCR, we do this in our sleep. This can’t be that hard. We should help with testing, because we can’t leave our house because we can’t get tested, there are no resources.” And so we worked closely, we said, “Well, there’s got to be a way to do this that’s a little bit more scalable,” rather than the current methodologies, because they’re relatively small-scale, there’s a lot of pipetting involved, there’s a lot of manual labor — which is I think part of the reason why it takes so long. Imagine trying to take a thousand water bottles, pipette out a little bit from each water bottle into a new tube. That process is fine for maybe twenty samples, but once you’re scaling up to hundreds and tens of thousands of samples, it’s sort of untenable and requires either some automation or some tricks along the genomic testing pipeline.

And so we developed SwabSeq, and it’s called SwabSeq although we don’t test very many swabs. We actually do a lot more with neat saliva, saliva that people just spit into a tube and that was a way . . . There was a lot of problem-solving throughout that whole process, and I would say the genomic technology was relatively easily. The technology is pretty similar to a regular RT-PCR, the traditional fluorescence-based RT-PCR that most clinical labs run. There are three major differences, I’ll say. One is a readout sequencing. So it’s a digital readout rather than a fluorescence read-out, so that in theory enables a little bit more sensitivity.
Because it’s a sequencing-based readout, we have primers that are unique per well of your PCR plate. And so those unique primers that are tagged onto the barcodes — the DNA barcodes tagged onto the primer set — those allow us to pull all the samples together once we’ve amplified the virus and then sequence it. And then we can deconvolute everything and we can figure out, exactly, based on the bar codes, which sample was positive or negative. And then the third thing: So as a genomic technologist, if you had told me this, I would have said, “Well, you have to normalize all of your values and then you’re going to spend all this time normalizing the DNA or RNA across your samples before you amplify.” And we get around that using endpoint PCR, and we include what I call a standard. So it’s essentially a little piece of the virus that we try to amplify that our primers amplify. But we’ve synthesized it, so it has six base pairs that are reverse complemented in the middle, and that allows, due to our sequencing readout — we can actually detect whether our primers worked and how well the amplification within that well is. So we have an in-well normalization that allows us to really be a lot more accurate with our quantitation. Our quantitation is a ratio compared to the Ct of a regular qRT-PCR.

But that technology, we’ve had that for a long time in genomics testing. It had never really moved into clinical lab testing because it’s sequencing, it’s complicated, the FDA doesn’t have a good way of regulating that. And just bringing up genomic testing in a clinical setting just has a lot of extra regulatory challenges that haven’t been fully worked out yet. There’s I think a lot of challenges in trying to, one, get that testing out there into the world. But I think the bigger challenge, it’s not necessarily the testing, but the bigger challenge is really logistics. Because of the way our health care system is designed, it’s really just not that easy for people to come and deliver samples to us. That operational logistics of testing, getting them to a specific site for the scalable testing, I think, proved to be one of the harder challenges.

And then the other challenge we had was we needed this process to be so simple, we had to go ahead and design our own swabs that had break points at specific sections. If we wanted to scale it, we needed to have the same tubes used for both saliva and nasal swab. And that worked really well and still continues to work really well, but has a lot of interesting other challenges when you’re trying to 3D print swabs or to manufacture tubes from different sites. Even companies that sell us their tubes that are automatable, different lots have different efficacy as far as how easy they are to open. And so with automation, you have a different set of challenges that we’ve come across in this particular process. But the technology, I think I’ve always said, is fairly straightforward. It’s really just the logistics and how do people pay for a test, how do people get testing. In Los Angeles, we’re a huge — ten million people — but it’s a huge county: How do we get tests
into one location? We didn’t have that infrastructure in place, and I think it’s a little bit better now, but still leaves a little bit to be desired given the rates of COVID right now in Los Angeles.

**PNS:** As we talk about genetic testing and use of big data sets to really, I think, ultimately inform clinical decision-making — because that’s why we’re all here, we want to obviously improve human health, that’s the whole point of doing all of this — would you be kind enough to reflect and maybe more forecast on where you see this integration of large data sets going in terms of informing clinical decision making? Where do you see artificial intelligence maybe fitting into all of this as we become more and more sophisticated in diagnosing rare diseases, or even common diseases, and making clinical decisions?

**VAA:** That’s a really great question because we are just . . . In genetic-based testing, I think we’re just in our infancy. We have a lot of data. Millions of people around the world have had their genomes fully sequenced. But I would say that a lot of the data that we have right now is very European-centric. And so that data is there, and for certain groups in our population, we can make pretty good predictions for things where we have a lot of data, things that are quantitative, like LDL levels or risk of heart attacks that we have a lot of data in the electronic health record [EHR]. But I think a lot of that, it’s not as strong in populations that aren’t as well sequenced, where we haven’t done those studies in enough individuals to see even the smallest effects of a specific variant in our genome. And so I think there’s still . . . I think a lot of people have noted this, and there’s a lot of work being done trying to improve equity amongst genetic testing, particularly in who we’ve sequenced and trying to make sure that we’ve included all groups and we’ve really taken into account all the different variabilities around what I’ll say is like genome-wide association testing — so those small effects.

I think the groups that have come the farthest have been in cardiac testing, risk of heart attacks, and increased lipids, so hyperlipidemia. But there’s still a lot more work to be done. So in the rare disease spaces, most of the individuals who are able to access genetic testing come from individuals of higher socioeconomic background, and so we don’t have a lot of data on how these specific variants might act in other populations and underrepresented populations. And then I think even sort of more broadly, when you think about genetic testing in the EHR, what I learned about genetics in medical school is very different even — and that wasn’t super long ago, it was long enough ago — but it’s different than what we’re able to put out now, the types of reports people are getting and the types of direct-to-consumer genetic testing that are out there. And so I think there’s still a huge need to educate the physician and the health care provider workforce on these types of tests and when to refer.
I think artificial intelligence can help us in some ways, but there’s still . . . We need to make sure that the tools we have and the data sets that we’re feeding into these neural networks and these artificial intelligence are also equitable and diverse, so we’re just not replicating the inequities that currently exist. We’re just not replicating them and not realize that we’re doing that when we put them through these artificial intelligence. And don’t get me wrong — I think there’s a place and it’s going to really revolutionize the way we do health care, but we just need to also take a step back and make sure that when we implement any of these systems, that they actually do what we think they do rather than replicating existing structures.

PNS: Well, as we move forward in the field of genetic testing, we’re certainly going to be looking towards you and your team and others in leading the path for us. I sincerely want to thank you for taking the time to share your journey as well as your perspectives on genetic testing. I know it means a great deal to the ASCI to have someone of your caliber joining the membership. And of course, we wish you the very, very best for the future. Thank you so much for taking the time.

VAA: Of course, of course. Thank you so much for having me.