## **SEASON TWO: Episode 32** Precision Medicine is Here: Dr. Barbara Fortini Helps Prepare a New Generation of Scientists to Apply It

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Karan Cushman: Welcome to season two of the Precision Medicine Podcast sponsored by Trapelo. This is the podcast where experts come to discuss the problems oncologists, reference labs, and payers face as precision medicine grows and consider solutions for advancing the quality of patient centered cancer care. Be sure to subscribe at precisionmedicinepodcast.com to get the latest episodes delivered straight to your inbox.

Jerome Madison: Thanks for joining us for another episode of the Precision Medicine podcast. I'm Jerome Madison, Vice President at Trapelo and I want to first of all pause and thank our listeners who continue to grow and tune in to the podcast for now over 30 episodes. We really appreciate our listeners and your feedback and your ideas for conversations or episodes. And the reason why I believe that you tune is because we have such great guests with really valuable perspectives. And today we have Barbara Fortini PhD, the Program Director for the Master of Science in Human Genetics and Genomic Data Analytics program at the Keck Graduate Institute, Claremont, California, which I did learn is the only graduate school in the US with the sole focus of scientific research and life science education.

Barbara, thank you for being a guest on the podcast.

Dr. Fortini: Oh, thank you so much for having me.

Jerome Madison: We met at the Precision Medicine Leaders' Summit West, and I love going to Barbara, these think tanks, these meetings, because the panels, it's really a way to crowd source ideas and to solve problems, right? So you spoke on a panel that addressed creating a new vision for health science education and I guess impending challenges, right? With preparing and supplying a workforce as precision medicine grows. And you're very much on the front lines of this with your leadership role at Keck, but can you start with just sharing a bit of your professional journey and how you came to lead this program at Keck?

Dr. Fortini: Okay. Yeah, so I have a PhD. I have trained in the classical science model. I did both my undergraduate and graduate studies at Caltech in Pasadena. And my graduate studies focused on both biochemistry and genetics of genome stability. So I've spent many years of my life, I won't say how many devoted to one protein called DNA2 which is involved in both DNA replication and DNA repair. And so I had a very traditional PhD where I did a lot of in-depth experiments on just this one protein and its one or two steps in DNA replication and DNA repair. And it taught me a lot of very important skills on how to understand problems at a very deep level and how just the biochemistry really directs everything that goes on in our genome. But when I was looking for my postdoc, I did want to switch it up and do something different.

So I did my postdoc at the University of Southern California, Keck School of Medicine in the department of preventive medicine. And I was doing a genomics project on colon cancer risk. And this was my first real introduction to genomics and how consortium level studies were doing experiments that we could not do in the past. There was no technology to do these kinds of studies where you actually do a GWAS and you'll have 100,000 cases and 100,000 controls and you do genetics at that scale where we could find regions of the genome that are associated with colon cancer risk. And it's really a statistical result. And the role that I had in the research group was to do, "The biology." I had to figure out why this particular region had some association with colon cancer.

So we worked on several different regions of the genome. It was lots of fun because in any given day you could work on a totally different project, but it really started to teach me that we can actually understand how the genome works outside of just being a source of information, right? So the genome has data, it encodes data, but it's also a three-dimensional molecule that moves and changes and it's modified. And so now through genomics we can actually study those questions. And so I really got into genomics. I started to appreciate how fast things move. I mean there were times where I would be asked to interpret some data, I'd write up a few paragraphs, do a couple experiments online, do some research. And this was published in the next month. We were doing papers every month because we had so many collaborators that really used their expertise and we would just hand around these files, the bioinformaticist would do something and the statistician would do something and then the functional people would do something.

And because we had this collaboration, our papers have 150 authors on them. But we could also churn them out very quickly because there was no one person that had to understand and be an expert in every single thing in that paper. And that's a big change to how science has been done for centuries, right? It's not just the single person toiling away in their laboratory with a Bunsen burner. And so it's a different kind of education and training that is needed to teach people how to do this kind of science. And this of course now is starting to make it into the clinical realm. A lot of this stuff even five years ago was thought of as just research, just pie in the sky. It will be decades before this is actually in the clinic. And that's not true.

Things are already starting to go into the clinic. We have companies that are now using RNA-seq in conjunction with their DNA tests. This kind of promise should not just stay in the ivory tower for the next decade. But we do need to understand really what's going on before we start treating patients with this knowledge and actually understand what kind of data we're really dealing with. And so that's how I got back into education. I really wanted to teach. I was one of those scientists that sometimes gets a black mark because I enjoy teaching.

So after my postdoc was completed, I went to the Claremont Colleges, the undergraduate colleges where I was a visiting assistant professor for two years teaching genetics and teaching intro bio, and I really wanted to reenvision how it worked because I looked at the syllabus that we're using in undergraduate genetics classes and it hadn't really changed in decades. We're still talking about the Hershey–Chase experiments and how we know DNA is the molecule of life. I'm like, "That's great. And there's some scientific benefits for students understanding how that worked and how innovative those kinds of experiments were." But we've learned a lot in the last decade. Why don't we spend most of our time talking about this stuff?

But it's hard. It's hard to make a classroom scratch. It's hard to decide what is the important stuff for things that are new. It hasn't survived the test of time. Some of the things I tell my students might turn out to be wrong once we have better and more accurate tools. But I don't think we can just stay with the model that I'm going to teach the students what I learned when I was a student because things are just changing too fast.

Jerome Madison: Well, I think it's interesting that in your early work you guys created a micro economy with this industry. The way you were solving problems and how collaborative you were.

Dr. Fortini: Yes, it's definitely a thing that I love about working in genomics. That of all the sort of pieces of science I've seen either through myself or my friends that have moved on into different aspects of biology, it's just amazingly collaborative in genomics and I think it's something that must have started from the very beginning. People work together, people share data, there's still amidst challenges, how to share data appropriately, how to make sure we're not accidentally double counting the same samples. But we've really been able to do a lot because we can get these big data sets together and the only way that happens is by people working together to enroll participants in these trials all over the United States.

Jerome Madison: So at the Keck Graduate Institute, what kind of students are seeking these graduate programs, and what are the opportunities that exist for those who complete the program?

Dr. Fortini: Right. We have two programs in genetics and the first is the Genetic Counseling Master's. So Master of Human Genetics and Genetic Counseling. And this is a very popular degree program in the United States right now. I think it's an excellent choice for a lot of people. Genetic counseling is becoming increasingly important to patients as we use genetic data to make healthcare decisions. We need to explain that to our patients because it has implications not just for them but for their families and for their future children. And this career has always been a very important part of the medical landscape, but just because of the explosion in genetic technology, there is such a need for genetic counselors. I've heard statistics like there's three open jobs for every graduate. There are less than 50 programs in the United States that are accredited. We don't want to just massively expand them by tenfold, we want to ensure high quality education.

So it's going to be a bottleneck for years to come that there just aren't enough training positions for genetic counselors. There are some challenges to training more just because the genetic counselors that are working are swamped. And so convincing them that they also want to take a student can sometimes be difficult. Sometimes the genetic counselors really want to take a student, but their manager needs to be convinced that they have time to take a student. And so that degree program has just a built-in population of students that really have heard about this career and they want to combine genetics and helping people and they really want to be a genetic counselor. So we have many applications for each one of our spots and unfortunately, we just can't take every qualified individual. And so when we were setting up this genetic counseling program, and that's when I came on board at KGI, this idea got floated out there.

Well what if we had a second-degree option that didn't require taking a genetic counseling board license at the end? The exam? And we just taught people the skills that are being sucked up by industry because a lot of people who get these genetic counseling degrees and licenses end up working in laboratories and for companies not actually counseling patients directly, but so you don't need a license for that. And so we just decided, okay, what are the skills that are needed? Why are these genetic counselors being hired by drug development companies? Well, it's because of their knowledge and training. And so we thought, well let's make the ideal candidate for that kind of job, that new job where you need to understand genetics, but you also need to understand industry. You need to understand product development. You need to understand how information gets translated to people who aren't experts in genetics.

And that's where we built the Genomic Data Analytics program, which I do have to compliment KGI of letting me run with it. I came on just to be a professor for the Genetic Counseling program and very shortly within a year we're planning out the second degree, which was as a professor is the greatest feeling in the world to be given a blank sheet and be told like, "If you could redo your whole education over again, what would you learn?" So we just sat down. Like, well, I need to know how to program in Python and did not. And I also need to have taken medical genetics and cancer genomics and molecular genetics. And one of my first, before I took the job, I said, "I have to be able to teach an entire semester on genomics in addition to genetics." And I don't know that the Dean actually understood what the difference was, but they could tell how passionate I was about it.

And so they said, "Okay." So we teach a full semester of human molecular genetics and we teach a full semester of human genomics in the first year, just to sort of instill in our graduates the mindset of both the single gene classic understanding of how diseases work to now the new way that we understand how the genome accomplishes all of this. And so this has been incredibly fun for me to be able to design a program, to really think about outcomes, to lay out together a curriculum.

So we did have some classes that were already being offered at KGI in our Master of Business and Science that I could pull from. But we also did get to just set out the whole curriculum week by week. What are our learning goals that we want to hit in this class? What do we want them to know before they get to that class? Definitely trying to put everything in the correct order and I will say we're still getting it right. We have had our first cohort go through their first year and the first semester of their second year, but until May we ought to have run the whole curriculum through two years, we're in a process of constantly revising that.

Jerome Madison: On the clinical side, I've witnessed this slow and deliberate adoption of the precision medicine approach to treating patients, building companies in the industry over the last 17 years. And I guess three major sticking points from where I sit. First it was the data or the lack of it. And then once we started to build data, retrospective analysis, prospective real-world data, it's now how do we use it? When do we apply it? It's clinical utility. And now it's even more operationally. How do we treat a system to expand its use? I mean you talked about like the deficit of appropriately trained talent, the shortage of genetic counselors. But as hospitals and healthcare system starts to think about building precision medicine programs, what needs to happen in order to overcome these challenges to meet the demand for the patient? Great patient care.

Dr. Fortini: Yeah, that's a great question. I'll start with your first, when the data, we're still collecting the data and I think we've been doing genetics for a really long time. But we've only been doing genomics for really and truly a decade or two. I was in college when the genome was released. I remember before that we had a few sequences of particular genes and you could go into NCBI and look at a few of them. But just think of, we haven't actually had the sequence of the human genome for very long. And even then, the first few years we had three examples, four examples, we hadn't actually sequenced a representative percentage of people. We're still trying to get sequences from people of all ethnic backgrounds. So we're still at the very baby steps of actually understanding the genome and getting enough data to do some real analysis.

That said, even just scratching the surface, we're learning really important things that have direct application to the clinics so we can't stop and wait until we figured everything out. And that's not how medicine has ever worked. If we have lots of things that we do that are not exactly as evidence based as they should be, but we do them in the best interest of the patient because we can't tell someone like, "Oh, I'm sorry you have cancer. Maybe in 10 years we'll figure out what the best thing to do is. So let's wait." We just can't, we work in reality. And so we're now starting to get enough data to make a few strategic applications. But again, we do have to scale up and we have to implement.

And so I think there's a lot of good work coming out of our major medical centers. I have to acknowledge my friends at the Rady Children’s, Genomic Institute for their Project Baby Bear. Where they've shown if you do very focused specific things with good criteria, you can have an impact on those patients. And then as we expand that and make it available to more patients, we can still continue to refine the process. But we do have to decide how is this work going to happen? It's at the current place. Things like Project Baby Bear, they're very small teams that are still run by the scientists that are inventing the technology. It has to get to a level of maturity where you can just have people train to be the operators that it's no longer the people that are inventing it that are the ones doing it. And that's going to take education, and that's going to take just some time to figure out what the best practices are.

But it's going to be quite a road. And I really feel for the people who don't live somewhere where they can come to a place where there's leaders, like if you're outside of Boston or San Diego, there's not that many options. You don't even know that these services are available and so the advocacy part and making it equitable that has lagged behind and it will still be a challenge. It's a challenge throughout all of medicine very simple things and it's going to be an even bigger challenge in precision medicine to try to make sure we're being equitable and that we're considering how we can bring this to every patient, not just the ones that can come to the place where these things are pioneered.

Jerome Madison: Yeah. Hey, really quickly, for our listeners who are not familiar with the Baby Bear program, can you give a brief overview and we know that same program has also been put in action in Florida with Baby Dolphin and I think in Michigan with Baby Deer, well, can you explain very quickly for our listeners what that is?

Dr. Fortini: It's a program from the Rady Children's Hospital that identified infants that were acutely sick within their first week of life and they couldn't through the standard diagnostic journey, figure out what was wrong with them within this week. And so it was a parallel program so they continued to go along the pathway that traditionally NEO and NICU would go through, but they also used rapid whole genome sequencing for these babies. And so within their first week of life they had been whole genome sequenced and looked for any clues to what was wrong in the children that way. And they found, I don't have the statistics in front of me, but it was roughly half the time they can make a different clinical management decision based on this whole genome sequencing data. And that improved outcomes, there were definitely changes to care. There were some children that survived that perhaps would not have survived.

And it's just been an exciting case study of if you are doing whole genome sequencing on the right population, you can actually change the prognosis for these children. And it's just, you can go to their website and watch stories. And I've been at a meeting where they were telling the story of a very, very sick child who was just continuing to get sicker and sicker and sicker. And they gave the story of doing the sequencing and finding the problem, which is a mutation in a gene that had never been documented in patients before. But it had a very simple treatment because it was something that we had a drug for a different condition that could affect. And then the next thing they let the kid run out onto the stage, right? So it's just amazing the impact you can have for those families.

And so the question is, how do you scale that up and offer that to any child that's born anywhere in the United States or anywhere in the world? For that matter. And so Project Baby Bear was through the state Medi-Cal system, which is for those without private insurance. And they ran this trial where you did not have to be at Rady Children's. It could be at any, I believe five different hospitals that they would do the sequencing, do the interpretation and then provide the recommendations to the doctors on site.

And again, great results. And that's the one thing about sending data back and forth. You don't actually have to send a patient's sample, you can just send the sequencing files and have someone interpret it, make a recommendation and send it back to the medical team. And so that is how it's being expanded to other states. And I really hope that it can expand past that very soon. But of course we have to have the analysts in place. The turnaround time is amazing. They do the sequencing overnight. They have some automated pipelines that prioritize, the genomics team goes through it and analyzes the data that morning and they can have a report in the hand of the doctor within 24 hours. But that takes a lot of people. And so we need more people with those skills.

Jerome Madison: Yeah. And the amazing part is that genetic information is a part of their medical record for the rest of their life and it's amazing the potential of what we could do with that information if that became a wider program for people at birth.

Dr. Fortini: Yeah. There's also some downside to that of course, we do have incidental findings when we sequence these children. We might find something that the person does not want to know in adulthood. Of course the babies did not consent to this, their parents consented on their behalf. You could talk about the ethics of whether they really have a choice to consent. You have a newborn baby and it's sick are you really going to think about whether you should or shouldn't do that? You're of course going to say yes to anything. But there could be something like BRCA1 mutation, right? That they find through this sequencing. Do you tell that kid? When do you tell him? Would you tell her when she's 18? Do you tell her that there's some information, does she want it?

There are a lot of issues that we haven't thought through as just a society on what we want to do with this information. And if sequencing becomes extremely routine, which I believe it will. We do have to kind of sort out how we're going to use the data to assure people we're not going to discriminate against them. It's kind of a slippery slope towards the mistakes we've made along the eugenics pathway in the past. It's important that we remember that this data always needs to be used for the benefit and at the consent of the patient.

Jerome Madison: Yeah. Very well said. Very well said. I'll get you out of here on this one. With thinking about the industry side because as you mentioned, that's become a greater demand for students. On the industry side the scientific and technological advances have turned what was once considered impossible into everyday tasks with discovery and what we can do and companies are having to rethink how they leverage the existing talent that's there while also thinking about the knowledge and skills they need to hire. In your position, what knowledge and skills do you see from an industry perspective are most in demand?

Dr. Fortini: That's a great question. We do have partners in the biopharma industry. We just received a very generous grant from the Amgen corporation to set up the Center for Training in Applied Genomics because everything in biology is driven by genetics now. It's a huge source of information and they would be remiss not to try to use that information. And so one of the biggest demands for training in genetics is in managing clinical trials and just developing new interventions. Because we do have all of this genetic knowledge now we should use it to make smarter, better drugs. But then we have to test it and we now understand that these drugs could be used differently based on your genetics, so the whole industry of pharmacogenomics. And so when you set up a clinical trial now, you have to make sure you don't accidentally set up a genetic trial.

You'll need to sequence or genotype all of the people in both groups to make sure there's no [inaudible 00:25:59] and stratification between the two. And that means that they need expertise in-house on a population genetics. They need expertise in-house in molecular genetics. And so we very much have thought at KGI on how to train existing professionals, people who graduated more than five or 10 years ago that want to know this knowledge. I will say every time I meet a genetic counselor and I talk about my genomic data analytics program, they all say, "Oh, I wish I could take those classes because it's the future and everyone knows it." But unless you're a student, you don't have access to that opportunity. And so we're trying to think about executive education, how we can make it work. Is it going to be online? Is it going to be hybrid? Do we want to do continuing education for doctors? And if so, what modality works best for that?

But these programs are definitely in the works at KGI and we would love to build partnerships with people to really understand what the best delivery method would be? We know everyone's busy and we know people want just the most important information. But it is one of these things that we know so much now about the genome to really understand any one piece of it. You do actually have to understand a lot of things. And so it's not something we can just package into a 10-minute TED Talk and now you know everything you need to know about genomics. So that's the challenge for us as educators is to figure out how to meet this delivery challenge and to inspire people to want to get to this education in a way that is directly useful in their jobs.

Jerome Madison: Yeah. Well, you have the soul of an educator because you mentor and inspire people and when you talk to someone like yourself, when I talk to someone, like you said it motivates me to know that as much as I think I know I need to know so and learn so much more. There's so much more to learn.

Dr. Fortini: Yeah, and I think what's amazing is how engaged and interested young people are. When I talk to people who are in high school, they're doing a lot of genomics and genetics in high schools now. Even in elementary school they're doing sequencing projects now that the Nanopore MinION is so inexpensive. You can do DNA sequencing with a group of elementary school kids and in high school they're doing these projects, so I don't worry about the next generation. They are really inspired and they want to do these degree programs and they're just are so revved up to completely solve all of these problems.

The bigger challenge is to get into those busy professionals that also want to know this information but don't have years of schooling still ahead of them to make sure we can get it in bite-sized pieces that will actually help people. I know that the public is definitely demanding this information and they expect their doctors to know it. Just the popularity of people doing 23 meets style sequencing and then expecting medical information in those reports and then asking their doctors to interpret it for them just shows that the public is on board and the future's on board. So let's just get everybody up to speed.

Jerome Madison: Well, thank you for the work you're doing and the impact you're making on the industry. And thank you for being a guest on the Precision Medicine podcast.

Dr. Fortini: Oh, thank you for having me. It's been a blast to talk about this stuff.

Jerome Madison: Very cool. Yes.

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**About Our Guest**

**Barbara Fortini, Ph.D.**

**Assistant Professor of Genetics/Program Director, Master of Science in Human Genetics and Genomic Data Analytics (MSGDA)**

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Dr. Fortini completed her Ph.D. at the California Institute of Technology where her thesis focused on the biochemistry and genetics of genome stability. Fortini undertook her postdoctoral training at the University of Southern California, Keck School of Medicine in the department of Preventive Medicine using post-GWAS functional genomics to understand colorectal cancer risk.

Fortini currently teaches courses in Human Molecular Genetics, Human Genomics with NGS Lab, and Functional Genomics for both Genomic Data Analytics and graduate students studying genetic counseling. She concurrently conducts research on genomic variants associated with colorectal cancer risk.