I'm Howard Lawrence McLeod. I'm the medical director at the DeBartolo Family Personalized Medicine Institute at Moffitt Cancer Center in Tampa, Florida, and I'm a senior member of the Population Science Group there at that institution, and a professor at the University of South Florida.

I was born in Tacoma, Washington in -- on August 1, 1965.

So my work in genetics was not directly inspired at all by my upbringing. I grew up in a home where my dad was a professor of computer science -- but did not bring his work home so he had computer illiterate children -- and a mother that was a homemaker and then was working in the school district after the -- us kids were all into school. And not really in the medical area, but always interested in it. And as I looked for a job at 16 years of age I happened across a pharmacy and they gave me a job cleaning the floors and filling the bottles -- the bins with bottles. And that inspired me to see how science could be applied in health care and really led me to go into health care in general. But I knew once I did pharmacy school and then my clinical pharmacology medical training, that there were a couple things that would never be important clinically. One was immunology and one was genetics. They were just things we had to learn to get to the real meat. And then as I got more interested in the clinical side and started expanding my research, I sudden realized that these were really important areas. And genetics, in particular, found me as opposed to me finding it.

So I did my undergraduate degree in pharmacy at the University of Washington in Seattle, which at the time was a five-year degree and it was a mixture of what you think of classically as pharmacium [spelled phonetically], making pills and counting them and all that, and what was now considered clinical pharmacy. And then I went on to do secondary training, a Pharm.D. degree in Philadelphia at the Philadelphia College of Pharmacy and Science, which was affiliated with the University of Pennsylvania Health System. And that's where I started doing more of the internal medicine aspects of training, but really not a lot of research. I had a little bit of research exposure as a kind of an afternoon/evening-type job.

But I then went to do specialized training in oncology at St. Jude Children's Research Hospital in Memphis. And at that point I got to see the science could really make a different in the clinic and it really got me into the research side of things. And ironically, that's where genetics found me in that we had some children that we gave the normal dose of chemotherapy to and it nearly killed them. And as we tried to figure out why these children were so sensitive to these medicines, we found that it had a genetic -- there was a genetic cause. A single base out of 3 billion was abnormal and it caused the normal dose for everyone else to be an overdose for these kids. And so that sort of training really led me to genetics.

I was not. And as someone who got pulled into genetics, I really wasn't in the mainstream in terms of knowing that. I'm sure my mentors knew about it, but I was a fellow and just trying to get by. And back then it was find the abnormal phenotype and then use the phenotyping to try to find the genetic cause. So it was very much a different approach than we would take now, now that we have the draft of the whole human genome.

So really the interaction between the patient's genome or the target genome. It could be a virus or it could be a tumor or it could be something else. And the drug therapy is what we're talking about. And so, back in 1956, Vogel coined the term pharmacogenetics and so it started with that. There are examples of genetic interactions -- or genetics being ascribed to pharmacologic interactions even back into ancient Greek times. But the term was really coined in the mid '50s. And it was really kind of a term that didn't have a lot of meat behind it for many years. And then as -- you know, in the '90s as genes, single genes started to bit's found, single variants in single genes to be associated with some abnormality in pharmacokinetics or in the pharmacodynamics of a drug, then we started getting some understanding that -- you know, that what pharmacogenetics really could be. And then as we moved to the era where you're looking at multiple genes, pharmacogenomics became the trending term. And functionally in the current times, either term means about the same thing. There used to be a joke that pharmacogenetics means you are over 40 years of age. Pharmacogenomics means you are under 40 years of age. And, you know, there's different things like that. But pharmacogenetics used to mean drug metabolism genes and pharmacogenomics, everything else, but really nowadays anything that's part of the human genome is -- and interacts with drugs -- is under the term pharmacogenomics.

And there was a point in time when people were very worried about which term you used. Like around 10 years ago, as you said, you know, people, you know, were passionate about which one they were. And then nowadays people are more focused on, you know, what are you doing as opposed to what are you calling it.

So I -- there was a fellow a year ahead of me that went to -- after training went to Nice for one year in the south of France and had a wonderful year professionally and personally. And so I decided -- my wife and I decided we were going to go to Europe for a year. And we were going to go to Nice also. But my wife couldn't work in France. She was an occupational therapist, wanted to work at that. In retrospect she wished she had just spent a year lounging in the French Riviera, but that's a different story. So we had an opportunity to go to Glasgow, Scotland. And so we decided to go there. Of course we arrived and we couldn't understand anyone, so we might as well have been in France. But there started getting exposed to the large, centralized cancer centers of Europe, which were very different from what the U.S. was doing at that time and able to have the volume of patients to really make a difference. Also we were -- at that point in time in the U.K. you were either a clinician or you were a researcher. And the two just didn't really interact very much. And so as someone who had clinical training and research training, I had the whole middle to myself [laughs]. And so it was phenomenal because both at the Beatson Institute in Glasgow, at the University of Glasgow, and then subsequently ended up staying there for almost eight years and subsequently at the University of Aberdeen. Really had that whole translational space to myself and with excellent colleagues. And that resulted in us being able to find patients that had extraordinary responses to therapy, either extraordinarily bad, as in severe toxicities that we needed to uncover the reason why, or amazingly good responses, when you had a tumor that should not normally be curable suddenly just melted away, and trying to understand well what is that? We also were able to institute what is now one of the largest cancer bio banks in Europe. Now back in the -- this was back in the mid '90s when bio banking was not really a passion of anyone's -- one of the pathologists at Aberdeen, Professor Graeme Murray and myself, decided, you know, we need tissue. We need to get it ahead of time. And thankfully there was an elderly woman who passed away and instructed her attorney to find some

innovative cancer research to fund. And so she gave us a large amount of money to start this biobank. And really that exposed me to the power of bio banking, which if you don't have the samples you can't make the discoveries. And so that was really a fortuitous aspect of really me being able to do some of the genomic work that we did.

Well it's true for all medicines, especially in the area of cancer therapy. The -- when you administer a medicine that your goal is to try to kill the tumor and depending on which medicine it is, it can also kill some of the normal cells or severely damage some of the normal cells to the point where it causes the patient to suffer. And so it could be something like a bad rash on the skin or it could be something like the entire outer layer of the gastrointestinal tract sluffs off and they have very severe pain, can't eat, and a higher infection risk because bugs can go from the bowels into the body and, you know, severe things like that. It's very common for some of the classical cancer drugs to cause the white blood cells to drop in number, causing the patient to be at higher risk for infection and even systemic infection. And so that's a concern. There are some toxicities like nerve damage that can occur from some of these medicines. And it's a real problem because there are times when the patient's tumor is being dramatically affected by the chemotherapy. It's starting to shrink away. But the nerve damage is so significant that the patient wants to stop. And this idea that we have to stop successful therapy because of normal tissue damage is just really frustrating. And it was a big driver in a lot of the genetic work we've done because we do want to know how to cure the patient, but we need to do it in a way that will not damage the patient to the point where their life was better before we got a hold of them. And that's really -- it's most dramatic in cancer therapy, but it's true for all types of therapy. You know, the high blood pressure medicine that one might take maybe it causes someone to be lethargic and not to be able to enjoy life in the same way or causes someone to not have the sexual performance that they might have had and you think, "Oh well, at least your blood pressure's controlled." Well if you decrease the person's quality of life, have you really done them a favor? And that's really a lot of the balance. So toxicity is really the normal tissue damage that -- the collateral damage, if you will, that can occur when you're giving a therapy.

Well, and good clinicians will understand their patient before they choose their therapy. And what I mean by that is that there are some patients -- so financially there are some patients that just can't afford that fancy new drug and want a cheap, old generic. And one can make that choice but also in terms of what the preferences are. So if someone's chief joy in life is playing the piano and you give a medicine that causes nerve damage so they can't feel their fingers, they can't play the piano. And really you're taking away joy while you may be slightly extending life in the case of advanced cancer therapy. So, you know, having that balance is really important. And you'll find -- you know, some of the oncologists that I admire the most when I've seen them in action, before the patient even knows it they understand their values. And so it might seem like the discussion is purely around the treatment of the cancer, but they've already ascertained what it is that drives them, what their social structure is at home, and those kinds of aspects that allows them to then craft therapy that will give them the best chance of controlling the disease but without taking the floor out from under them in terms of the other things in life.

Well, I think really throughout history there's been a need to distill data together to make decisions. And whether it's a research decision or a clinical decision or a policy decision, it's the same thing. And, you know, early on in my training there was less information to deal with, and

so one could take, you know, all 100 articles that ever been published on the topic, read through them in a rather fast manner, and distill it down into a nice, single malt, if you will, of information that one could ingest. But the -- as data exploded and as the literature exploded and as all these elements came out, it became literally physically impossible to handle all of the data. And so the databases that came forward -- the first type of databases that we used were around information. There's the National Library of Medicine, put together various versions of MedLine and all these other ways of trying to find literature. And right now, you know, most people training or even just the general public, don't even realize that you didn't used to be able to do that. So to be able to get online and to do -- put in a search term and find something through PubMed or through Google Scholar, whatever your favorite term is, is a huge advance that is really taken for granted these days. Another one that was a huge step forward was a database called Gene Bank. And it was something that, in my mind at least, was really spun out of the Human Genome Project. It may have had other origins, but I link with the Human Genome Project. And that, if nothing else, became a catalog for different sequences of DNA. It might be a 50 base sequence, it might be a million base sequence -- and I guess there weren't too many of those -- but you then could start doing things like more professionally designing your primers on which to do to preliminary chain reaction to pull out a gene of interest. Or look -- and as different species came out, you know, as someone who's dealing with humans you might say, "Well, who cares if the cow genome was done, or some other genome." Well what became very valuable to me is as we started to try to understand families of genes, maybe only one family member was sequenced, we could take that sequence, compare it to other species, come up with regions that seem to be conserved across the species, and then use those as primers to amplify the things that are in between and start capturing family members. And using -- we ended up inadvertently using a lot of the other mammalian genomes, in particular, to guide our degenerate PCR, if you will. It was the primers that would be less specific, allow other versions to come into the reaction in order to find new findings. So, you know, we knew a little bit about a gene, we could then go and sequence it up or PCR it up and sequence it and find out some of the rest of it. And then as the Human Genome Project started maturing further, that, you know, Gene Bank became very full, other databases came out that had that similar information. And then it became just a normal part of daily life. If we were going to do some sort of research analysis, these databases were the underpinnings of our science. And I would argue that the reason why advances have happened as fast as they've had -- and I know people think they haven't happened fast enough, and I think we all wish they'd happen faster -- but the advances that have happened have happened much faster because of the databases, both the data that's in the databases and then the also continuous reminder that we need shared science. And I don't mean in some Marxist sort of way, but I mean there are certain precompetitive elements that help all of us do our work better. And so I might be working in a certain area and I might want to be just the best in that area. But by having this central repository of information, whether it's the genomic sequence or whether it's sequences from different species, or whatever it's the Encyclopedia of DNA Elements or whatever it might be, that sort of thing helps inform the kind of they're doing. And certainly in my own area we've made advances much faster by having databases that were kind of foundational in the work we've done. And I think that that's something that -- they become so essential that we almost don't notice them anymore, but they really are important underpinnings for all we do.

Very much so because they caused -- they changed the culture of science. So I remember in the mid-'90s collaborating with one part scientist, who was a biologist that had been working on a gene that we have now found to be important for some drugs effects. And there was another person at another institution who also worked in that same area. And the fact that I was working with one person precluded me from working with the other. There was just this paranoid, competitive nature that was restricting advances as opposed to what we see now after these agreements where it's expected that you immediately share your data. It is expected that others will use that data regardless of whether you want them to or not. [laughs] And then they will find things and sometimes they will find things that go beyond what you found because they had a different way of doing it. But that becomes normal and expected and it totally changed the culture.

Yeah, the FDA's role has been very mixed. So in the genomic area there have been certain folks -- Larry Lesko, Janet Woodcock, [unintelligible], Mike Pacanowski, some of these folks at the FDA that have been -- I would call them almost advocates for pharmacogenomics or the use of genomics in drug development -- to the point where they have caused package inserts or prescribing recommendations to be changed even when the company didn't necessarily believe they should be. And they've really stimulated the field forward in that way. And then there have been other elements of the FDA -- and you'll notice I won't name names in this case -- that have really not been up on the regulatory science and the ways that genetics and genomes are being applied and didn't really see the value in them. And that led to a number of missed opportunities. If you look back in cancer therapy, there have been a number of drugs that have been approved and then in retrospect have -- subpopulations have been found to have -- where all the benefit was -- and then the package insert has been changed or the prescribing recommendations have been changes based on that. And it's -- it really reflected -- the data was known beforehand, but it reflected a lack of either understanding or desire on the FDA's part to make genomics part of medicine and make it part of the use of a medicine. The drug companies, they -- there's been also a real mixed group there. You have some examples and Alan Rose's when he was at GlaxoSmithKline was an example of somebody who decided that genetics and genomics was going to be a major part of what they did. And they have some huge successes. They were able to understand why some -- whatever toxicity was occurring in some of their drugs that allowed the drugs to get on the market with -- because they could show that it wasn't really liver damage, it was the presence of a certain genotype that gave an apparent signal of damage. They were also able to show that one of their HIV drugs -- anti-HIV drugs -- was causing a hypersensitivity reaction in about 5 percent of Americans. And they could show that by using a genetic marker one could 100 percent eliminate that hypersensitivity reaction. That became the norm. so whenever a patient with HIV has come to one of the centers I've worked at, they've had that testing done as part of their initial workup so when they do need that drug Abacavir at some point in time, their HLA B5701 marker, as it's called, was already in the chart and could already be acted on, and say, "Oop, we're not going to use that drug, we're going to use this other one instead." Ironically, at least what's been published in the public domain, was that there was a 40 percent increase in the prescribing of that medicine. Even though you've taken 5 percent of the patients away, you've now made it so that 95 percent that's remaining, there's a much greater confidence that it's going to be safe and effective. There was high confidence it was going to be effective, but it was the safety part that was of concern. Now that's been eliminated. And so this idea -- those examples have driven pharma companies to

look at genomics as a useful tool. But there's still, even in modern times, a lot of folks, especially in the marketing areas of pharma, that do not want to segment the population. They would like -- you know, in their mind 100 percent of the people are going to use their medicine. And anything less than that is a failure. In reality, if you can get 10 percent of the patient population to use your medicine, that's a huge victory. And if the genetics -- so if 30 percent use your medicine, you know, they should be jumping all of the place. So part of it is just kind of the realization and giving more examples out there, case studies so that they realize it can be useful. I haven't seen the FDA and pharma up until recently be a huge obstacle to genomics research other than they -- pharma tends not to share their DNA, and I can understand why, although it's a missed opportunity. And more recently the FDA, not so much the drug branch, the Center for Drug Evaluation and Research, but more the Center for Devices in Radiologic Health -- CDRH -- has tried to get into the fray a little bit on devices for genomics. And it's really been a bit of a mixed bag. They've introduced some burdens that are too great for the industry to bear and have stifled progress in some ways. They certainly introduced some expectations to researchers that have stifled research. But then they've also raised the standard in terms of the quality of the machines that are being put on the market. So it's kind of a mixture in terms of what their role has been.

So Bi-Dil was the culmination of two old anti-hypertensive medicines that also had activity in heart failure. And so by taking two olds medicines and putting them together in a certain formulation, one developed a new medicine that could be branded and sold as a branded product. The data had -- there had been data out there that these -- excuse me, these two medicines had better activity in African-American patients than in European-American patients. And the data was relatively consistent. It wasn't like 100 percent of African-Americans benefitted and zero percent of European Americans. It was more like 40 percent of African-Americans and 20 percent of European Americans. So it was a difference, a significant difference, but not an absolute difference. And so there was a decision made by the company that developed the medicine. And it was partly a decision based on the science and partly based on kind of a marketing opportunity. And that was they were only going to do the study in patients who were self-described as African-American. And they successfully conducted that study. They collaborated with the -- an organization of African-American cardiologists to do this study and were able to successfully complete the study, were able to show that this drug Bi-Dil was better than the comparator. And it was an important finding. The controversy came in a couple different ways. First of all, you now have a drug that's approved for one part of the population, but there's no data in the rest of the populations. So it's not like a medicine has been shown to harm people over 75-years of age and therefore there's a black box warning to not use it in that context. But rather, there's data in one group and then just no data. And so you didn't know whether it was going to be an amazing drug for your non-African-American patient, or the worst drug ever, or something in between. And so that absence of information was very unusual compared to the other ways of segmenting the population that had been used in the past, whether it was kidney function or age or drug interactions, or whatever it might be. The other element was that African-American is a social construct. It's a name that someone puts on themselves. I mean, other may put on them also, but in this case it was what the patient thought they were. And so that's fine, but when you look at the biology, you know, the liver function or the genetics, not everyone is -- has the same amount of ancestral African genome compared to some of the other people within the study. And so you saw some people who, based on the genetic architecture, were really 95 percent or so European-American, and others based on that same

architecture were 95 percent African-derived, mainly West African, was the comparators. And yet those people all had the same level. And there wasn't a lot of data on what was the absolute cause. So if you have a cause -- a causative variant -- a genetic variant that will mean the reason why someone responds to a medicine or doesn't, it can be used in any context. It doesn't matter what you call yourself, it can be used. Whereas, if you have this label, it's just basically how you were brought up and how you think of yourself and such. And so the massive heterogeneity amongst the African-American population in terms of genetics, in terms of organ function, in terms of other things, really made it so that it wasn't very precise. It was not really a good way forward. And some half-hearted genetic analysis was done to try to find the cause. But it really was not encouraged by the drug company, at least in my personal opinion. It was also not really supported by the NIH or other funding bodies. And so there are a couple of individuals who tried with the collections they had, but they didn't have definitive sample size, they couldn't really come up with the answer. And so, even today that medicine, which is not commonly used, but it's still available, is not really -- has not really been further refined in its use. And so part of its use is, you know, how do I know which patient to give it to? You know, typically most clinical practices of any type don't necessarily capture what the person thinks they are. And so one could say, you know, "Hey, are you African-American?" and then use their answer to go forward, but typically it's not really an important part of medicine practice, and so it's not asked. You know, typically gender is often inferred and not asked and I guess race or ethnicity could be also. But with gender, at least in our practice, we do a pregnancy test in our patients that say they're female and we believe them, to make sure they're not pregnant because the chemotherapy might harm a fetus. And so we have that extra objective measure because we really don't care whether they're male or female, we just don't want to harm a known fetus that happened to be present. And so, whereas when you're just getting someone's self-declared race or ethnicity, you're really not describing them very well. I think all of us know the golfer Tiger Woods. Now in the United States he's the most famous -- well probably the most famous golfer -- but also the most famous African-American golfer. In most of the rest of the world he's the most famous Asian golfer because he's 50 percent Thai -- his mother was 100 percent Thai. He's 25 percent African-American and 25 percent one of the Native American groups, I can't remember which one, Cherokee I think. So really he's mainly Thai, more of half Thai, and he's only one-quarter African-American. And yet someone in the U.S. might stick an African-American label on him, whereas in the rest of the world where they just don't think that way, they stick an Asian label on him because of that. So what -- if you're ready to prescribe a medicine for him, which part of him do you pick, you know? Do you pick the Thai part or the -- I mean, it just illustrates how -- the lack of precision by using some sort of social construct to apply it. And I'm not on some soapbox around, you know, "Don't use the term race." You know, there's going to be a label stuck on a part of the population of some sort. And so I don't really care about that argument so much, although a lot of people are very passionate about it, but I care about the lack of precision and the -- if we're going to use a label, it better be a label that's useful and this is one that's just not. And so it's kind of a long answer to your short question, but I think that there are a lot of examples out there where labels are being used, even in cancer. Colon cancer is probably at least 10 different diseases, you know. Every one of the cancers we know of now is a bunch of diseases. So really using the term colon cancer in modern times is really rather ignorant. We should be using a much more precise label in order to understand the patient and which therapy they need. But yet it still persists. Now colon cancers don't have feelings, therefore they can't express any anti-colon cancer label arguments. But

really it's just as much how we call disease as otherwise. Diabetes, I mean, that's a bunch of diseases and yet we still use one term. And so I think we're heading towards a time where a lot of these labels are not as precise. Now there are times where we have used these labels and that is where we've tried to use genetics for public health purposes. And so you might think -- so genetics for risk of breast cancer or genetics for the -- for -- whether you're going to succumb to Ebola virus or something, is one thing. But we've used in terms of how do you choose which medicines you purchase for your national drug formulary, you know, your -- the medicines that are available in your country? And the World Health Organization has something called the Essential Medicines List. And it's basically if you could only give a certain number of medicines, here's the list you should use. But the problem is they might have five drugs for your favorite disease. So if you have five drugs for asthma and your country can only afford two, what do you pick? Now, all five of these drugs were selected because they have fantastic efficacy, acceptable levels of toxicity, at least in the clinical trials that have been done, similar cost, similar access, similar ways of controlling. So they are a bunch of equals. And so if you can only afford two of them, you're stuck. It's not like one of them -- and if you're outside of Europe and North America, certain parts of South America, Australia, more recently China, your patients have not been subjects in the clinical trials. And so if you're in -- gone in West African and you're trying to choose the drugs for asthma, you -- all the studies, the beautiful studies that were done around efficacy and safety, had no Ghanaians in them. So you have no local context in which to make this decision. And so you just have to kind of stare and say, "Well, we didn't have a -- get a five-sided coin and flip it or something. What do we do?" And so we've used genetic information where it's been associated with adverse drug reactions, toxicity, or with altered efficacy and look at the frequency in local populations. So we looked at the five most common tribes in Ghana, for example, and asked the question, "Is the risk of bad events or the risk of good events different between these populations and what you'd see in U.S. white patients. And we picked U.S. whites not because I'm from the U.S. and white, but because most of the safety and dosing data is done in the normal volunteer studies that are predominantly U.S. white patients from that part. And so what you can find is that, you know what, this Albuterol, the drug Albuterol, as it's known to the rest of the country -- rest of the world, is the drug -- the main drug for in the U.S. Well about 75 percent of Sub Saharan Africans have a mutation in the receptor for this drug and are less likely to respond. So actually we'll take that one out of the mix and maybe there's another one where there's more toxicity, you start getting down to the point where you say, "All right, now we're choosing two out of the three that are remaining or something," and so you can now get into a much better decision. And it's really been useful in terms of helping developing countries do this practical choice because the most high-stakes aspect of their health system is choosing the medicines. They have very cheap facilities, no expensive equipment, low salaries, but the medicines, even generic medicines, are the bulk of the cost. And so they can now make it much more objectively for that. Also it's really taught us in the West that often the choice is not awesome therapy versus not awesome therapy. And you're trying to decide which one to give and it -- you know, it's going to be awesome unless you, you know, it has to be amazing otherwise. But rather, it's a tie-breaker. You know, you've got equal therapies and you're trying to decide which one is the right one. Well just a feather will tip the scale for that, just a little bit of data. And so in that way public health genomics has been useful to take groups within a country that are self-labeled and try to understand what's the best thing for that country, rather than saying, "Hey it works in Washington, D.C., we'll go ahead and try it out in Accra [spelled phonetically], you know, or wherever the country might be."

So the basic premise of that article -- and I know there's a lot more in it than this -- but the basic premise was that we were looking for things that we knew how to look for and not looking broadly at what the real answers might be. And so, you know, the old joke was, "If you have an assay for a variant in CYP3A4, that gene in your laboratory, it didn't matter what the question is, the answer was CYP3A4." You know, you had the assay running, therefore you were just going to churn as many samples through as you could. And what we found is a lot of papers saying, "Hey, this is associated with that." But when you dug into it, it was a weak association and it was heavily confounded by population stratification and other issues. And it really demonstrated that we were looking for things that we knew how to look for as opposed to stepping back and letting the biology tell us what the answer was. And certainly that is -- that -- since that time that has really panned out. There -- the discoveries that have been made in terms of robust markers that predict response to therapy or toxicity to therapy, none of them were the obvious genes. They weren't the metabolism genes necessarily. A couple of them were, but they weren't the drug transporters, per se. They ended up being an interleukin, like aisle 28B for the interferon therapy in the Hepatitis C context, that was not a gene on the list. It made biological sense when it was -- after it was found, but it was not one of the candidates. And so a genome scan identified a hit that turned out to be biologically plausible and turned out to replicate and be clinically useful, same with the Abacavir example with one of the HLAs. It was thought for sure that it was a metabolite or some sort of pharmacology issue, when it turned out as an immune system issue. And that sort of thing really has highlighted that in most cases we don't know the right genes. So we have to step back and find the right genes and then discover their utility or their further utility, try to refine that as opposed to just saying, you know, "Hey I'm smart. I know that this gene is involved, therefore I'm going to make it fit into this, you know, this hole." And so that's still a problem today where we still see papers coming out that really focus in on genes that we think might be important without a lot of data. And, you know, now there's becoming more and more genome-wide association studies, whole genome analysis, whole exome analysis that does step back and say, "Well what's the answer." And certainly you need a larger sample size and a lot more statistical power to get this statistical power to answer these broader questions. But you're going in and doing a bunch of small studies with a small number of genes. Basically all you have is publications, a longer CV, you know maybe you can fool some people that will give you some grants, but you're not helping grandma in any way, shape, or form. And so, you know, a lot of what we're seeing in 2005 -- and I'll probably be saying it in 2015, and hopefully not in 2025 -- is, you know, we need to be disciplined and let the biology tell us where the predictors of drug response lie and not just say, "Well I've run this diagram of how -- what happens with the drug, and so I'm going to make that," you know, "Here's the model. I'm going to try to prove the model," as opposed to, "Here's the data. I'm going to model the data."

So technology has played a big role, but there -- it's been ironic where things are headed. So right now we're getting -- we're able to analyze more and more of the genome at a price that can be afforded. So, you know, getting to the point where you can do whole genome now for -- you know, for -- well you -- a 30f coverage whole genome for about $1,000. And if you need it to be bigger, of course, it costs a little bit more. And those costs are going down, at least to some extent, although we're beginning to reach the point where the costs are mainly personnel and those costs are not going to go down. And so I think we're going to -- the costs are going to

plateau a little bit just because the people costs are going to be the main driver. But that -- for discovery, looking broadly is fantastic. And -- but there are some times when you go broad, you find the answers, or at least the majority of the answers, and then you actually don't want to go broad because when you look broadly you find a bunch of things that you have to explain that may have nothing to do with what you're looking for. And we've had the -- you know, we've had tumor that we've sequenced to try to decide therapy for a patient and then we've found a Parkinson's risk variant. Well we're trying to help someone, you know, cure their cancer and now we have to figure out how we talk to them about Parkinson's risk. And we didn't really consent them to even think about that because we didn't think about that, you know. And so these sorts of issues have come up with the technology. And so I see a real irony right now where there's an increase in chip-based technologies. And as people go and find the majority of what they want to find, they then could put it on a chip, where for $40 they can look for all the things they know what to do with as opposed to $1,000 to get the whole genome. And you think, "Whoa, on a step-by-step basis it's much more efficient to get the whole genome." Yes, that's true, except the informatics that happen on the other side of it are much more cumbersome with a whole genome or whole exome or even a GWAS chip than they are with a much more focused type of chip where you can really program in the clinical decision support on the other end and have it almost be a hands-free type of informatic pipeline. And so certainly the technology changes have been a huge boon for discovery, but we're seeing now a reversion back to this other way. And, you know, we've even suggested that the Cancer Genome Atlas, as it's finding all these variants, you know, so what happened with the Whole Exome Project? There was an NHLBI and NHGRI project where 25,000 whole exomes were performed in a number of different people. And then the variants that we're seeing at least twice in -- across these 25,000 people were stuck onto a chip and both Illumina and Affymetrix, those two companies, even today offer these chips that have these variants. And so one can do the equivalent of a 25,000-person whole exome type of analysis with a $40 chip or, depending on how many you're doing, the pricing could be different, but a cheap chip. The Cancer Genome Atlas could do the same thing. And, you know, we're encouraging them to do that where we can now have a Cancer Genome Atlas chip, we go in and we get all this data and suddenly for, you know, 100 bucks or whatever, we can get what otherwise would cost, you know, $1,000 or more and a ton of informatic time, but would not discover any novel variants that a person might have. So, you know, these tradeoffs between do we need to discover all of the variants and do we need to apply the known variants, is now kind of increasing the diversity of platforms that are being applied.

You know, I'm not part of the Cancer Genome Atlas in terms of, you know, I'm not paid for it, so I really don't have any extra ground in that standpoint, but I have found the Cancer Genome Atlas data to be incredibly valuable for two reasons. One, it gives us some context. When we find a variant in one of our patients we can now look back, both within our internal data because we have around 5,000 patients that we've sequenced at Moffitt, but also with the TCGA data and say, "Has this been seen before?" And even the fact that it's been seen before gives us some context in which to interpret their results. The other thing the Cancer Genome Atlas did, and a lot of that data is just now coming out, so maybe that's part of the lamp post argument, is that it made sure there was RNA analysis, protein analysis, a methylation analysis, MicroRNA. They looked at a number of the different types of omics. And so we're going to get a number of those variants put into some sort of transcriptional, and when possible, translational context and that is going to help us with this driver/passenger type of scenario, not perfectly by any means, but way

more than it was otherwise. The other thing this done is we've seen a lot of our basic science colleagues that might be -- maybe they've made it their life's work to understand a certain protein and they're really good at this protein. And that's fine except the question was always there, who cares? Do we really care about this protein? They can now take genomic variants that have been found in actual cancer patients, model those variants in their small systems, and come up with insights that not only help you understand the biology of the protein, but also what it might mean in terms of a patient effect of some sort. It's led to new screens. You know, there are drug companies now and academics that are screening libraries of compounds against targets they hadn't thought of before because of the TCGA. So I totally understand that we now have a bunch of lamp posts because of the TCGA, but those -- all those lamp posts are helping us see much more clearly than if we only had one lamp post. And so I would say, "Hey, we've got light now in which to ask these questions as opposed to before where we were just stumbling around and hope we accidentally found something.

Well I'm someone who was just kind of accidentally drug into genomics, chasing the cause for variability in patient response. And so I'm not a genomicist in that -- in the true sense of the word, even though I made my career applying it -- and so if it's blood level or if it's protein level or RNA level or shoe size, I mean, I don't care, you know, whatever it is that helps us understand the patient a little bit better and make some decisions, I'm in favor of. And so the -- you know, to me, the genome has a lot of answers right now. But, you know, as RNA and protein, et cetera start coming in being more practical, they'll be useful, too.

Well we're also hitting an era -- on that note, we're hitting an era where there's going to be a lot of application of genomics as a way of controlling variability to unveil dietary or environmental exposure type of functions. So, you know, genetics might only be 15 percent of the variability. Well let's control that 15 percent by accounting for the genomics and that opens up even more all these other sources of variability. And so the people who could care less about genomics in terms of, you know, the EPI folks that might be focusing on something else are going to find genomics incredibly useful as they try to really nail down the various causes.