Jean McEwen, and I've been a program director in the Ethical, Legal, and Social Implications program, or better known as ELSI.

In Minneapolis, Minnesota.

I'm not sure there really was much of anything in high school or certainly before that. I -- you know, I -- actually, I started out in Catholic school where we had like basically no science education, so I certainly had no scientific background. You know, did have -- the nuns kind of inculcated me in the importance of ethical reasoning and that sort of thing, but beyond that, there wasn't really much of anything, and through high school, I didn't really have a clear sense of where I was headed.

Yes, I was a philosophy major in college. I was -- interestingly, though, I never was interested in ethics at the time. In fact, I never took an ethics course. Even though I was a philosophy major, I was interested in philosophy of language and logic, took a lot of those courses for some odd reason. And, you know, began to take a bit more science. Still very much, though, you know, liberal arts or humanities kind of orientation. So, I was still a little bit skittish about the sciences. Did take a genetics course, though, for the first time in college, and that was very interesting to me.

Well, after college I really -- you know, didn't really know what I wanted to do. I worked, you know, kind of odd jobs for a few years and, you know, knew that at some point I wanted to go to graduate school, but to do what I wasn't really sure, I think probably like a lot of people from, you know, my generation. And a friend of mine one day said to me, "Well, you know, you like to write. You're a pretty good writer. Why don't you go to law school? You'd be a pretty good lawyer." And I just thought, "Oh, okay, maybe I'll be a lawyer." I mean, I gave that little thought to it, which, again, I think is probably not uncommon. Years later, when I actually was teaching at a law school, I realized that my story isn't that unusual. People go to law school for basically -- lots of times out of default, not really knowing what else to do, and that's what brought me there.

Well, I went to law school at Northwestern in Chicago and was interested in a lot of different areas. You know, family law. Children's rights were very interesting to me. And interestingly, during law school, I became interested for the first time -- or I started to learn about this whole kind of field of bioethics, which almost didn't exist before that. But it was like all of a sudden there was kind of like -- it was when the Karen Ann Quinlan case, which was, you know, the case of the girl who was in a persistent vegetative state, and it was a question about the right to die, and I thought, "Oh, that is really interesting." And then there were -- you know, there started to be these, you know, donor insemination cases, and so the first assisted reproduction cases, and then, you know, Louise Brown, the first IVF baby was born, and so there was lots of stuff about that. And so, I was really interested in those issues and they really kind of sparked my interest. But there weren't really law school courses about that, but I started thinking about, you know, those kinds of issues and thinking about them sort of in legal terms. But there weren't really courses to take, you know, in that area, and so it was just kind of an interest of mine, but not really something that I was pursuing in my coursework.

I practiced for a few years, basically -- you know, I needed some money to start paying off my debts. Knew pretty much right away that law practice wasn't something that I wanted to do forever. I kind of had the sense that I eventually wanted to teach, probably in a law school, though I wasn't quite sure, but that was sort of the direction in which I kind of thought I was heading. But I kind of figured that if I was going to teach I would either need to go and get an advanced law degree or a PhD. And I had, you know, again, been developing this sort of interest in these bioethics issues or kind of law and medicine kinds of issues, and there wasn't really -- or at least I wasn't really aware at that time of a program that exactly dealt with that sort of thing, but I became aware of a program at Brandeis University that dealt with at least issues that kind of dealt, you know, with kind of tangential issues, some health policy, kind of the broader health policy issues, and family law issues. And so, I decided to go there, again, just sort of stumbling in a general direction of where I thought I wanted to go, but, you know, just kind of stumbling.

So I got my PhD from Brandeis University, although that took many, many years. I basically went and completed my coursework and then it took me many years to get my dissertation written because -- even just to sort of figure out my topic was kind of a circuitous route to get there.

Well, so that's a bit of a longer story, because sort of how I got from my coursework to then finally deciding on a dissertation topic, which in turn relates to kind of how I ended up at NHGRI -- so, basically, what happened was that I finished my coursework, went back, did a judicial clerkship for a couple of years, and then ended up teaching at Boston College law school, teaching -- actually, just teaching sort of a legal writing course, but then eventually started -- got some opportunities to teach law and bioethics and family law. So, getting closer, you know, to the areas I was interested in. But that dissertation was still hanging out there. I still hadn't done it, mainly because I was working fulltime and didn't have a lot of time to think about the dissertation, but also because I didn't really have a topic. And I kind of, again, was drawn to these kind of bioethical issues, but I just wasn't quite sure sort of how to focus myself. And so, one day I literally -- it was completely sort of fortuitous. I was at a party with a friend and another friend came up to me and we were talking. And she told me that she knew of a guy named Phil Reilly, who was working at that time at a place called the Eunice Kennedy Shriver Center, which is -- this is in the Boston, Massachusetts area. And he was -- had just recently gotten a grant from the Department of Energy, which at that time has an ELSI program similar to the one at NHGRI, although much smaller. And he had recently gotten this grant to look at issues related to privacy and discrimination in connection with genetics. And she said, "Because there's this thing called the Human Genome Project and that's -- you know, he got this grant from Department of Energy, which is part of the Human Genome Project." And it was literally the first time that I heard about the Human Genome Project. And all of a sudden, it was like, "Oh, my God, this is really, really interesting. If I could get a job -- this guy says he's looking for someone. If I could get him to hire me, this could, you know, lead me in this direction that I've always kind of been drawn to but never could quite, you know, find the right kind of entrée point." And so, I went to talk to him and he agreed to hire me on. He -- I think I had done some research on privacy issues in family law. And so, I actually had developed a little bit of expertise in privacy law, so I think that was useful to him to have that on that grant. And so, what happened was -- is that I started working with him on that grant and we did some of the -- actually, the earliest studies on genetic privacy and discrimination. This was back like in 1990,

’91. We, you know, did a study of state insurance commissioners, you know, looking ahead to, you know, what kind of interests might they have down the road in using genetic information in life insurance. So, we were thinking ahead, you know, even back in 1990, to the possibility of this someday being an issue in the future. So, I worked with him on that and we then -- you know, we worked really well together and we wrote another grant that was focused on biobanking issues, and we got that grant, also from the Department of Energy ELSI program. And that then sort of led into my dissertation, because we were looking at all different kinds of biobanks and sort of ethical issues and what their policies were in terms of how they were dealing with samples and informed consent and all the same kinds of issues we still deal with today. So, we were looking at, you know, academic, commercial biobanks; we looked at newborn screening blood spots, even back then. We went and we talked to what was going on in all 50 states with their blood spots, researched that. Now, it seems all kind of ancient because, you know, we’re still dealing with these issues today. And then we also were looking at these forensic DNA databanks that they were starting, you know, where they were collecting the blood from convicted offenders and storing it and using it to solve crimes. And this was just in the very early days of doing this, so there were all these kinds of, you know, privacy issues and just all sorts of ethical issues connected with these things that we were looking at. So, the DNA forensic part of that work, I basically turned into my doctoral dissertation, so I wrote my dissertation on, you know, ethical, legal, and social issues connected with DNA databanks. And this was, again, very early on. I think there were maybe only 12 or 13 states at the time that had these. Of course, now all 50 states have them and they’ve been used to solve all sorts of crimes and that sort of thing. So, that’s a long story about writing my dissertation and how I finally, eventually, after years, managed to graduate with a PhD. I had to get several extensions of time from them.

Right, yeah. And I was still teaching at Boston College and doing some visitorships at other places, and so doing a little bit of teaching in the law and medicine area. But still most of my teaching was kind of in other areas that I wasn’t really that centrally interested in. And so, I was really interested in seeing if I could find a position where I could be focused more, you know, spending more of my time focused on these emerging issues in, you know, bioethics and especially in genetics. But, you know, for a couple years it just -- nothing was kind of going exactly in that direction. And then, one day, I was reading the American Journal of Law, Medicine, and Ethics, and I saw an ad in there -- this was in the days when they still had printed journals with printed ads, yeah. And I saw an ad for this position at the Ethical, Legal and Social Implications program at the National Human Genome Research Institute, which I was aware of because, again, my work before had all been through the ELSI program at the Department of Energy. But I was always aware that the NIH was where they had, you know, the bigger program. And you know, they were the people who really had the money and were really doing the innovative kind of stuff. And so, they were looking for a program director and I thought, “Oh, my God, this is just what I’ve always wanted to do.” And so, I applied for the position and I got it.

Yeah. Well, I was brought on for -- sort of for two things. One was to work, you know, generally as part of the ELSI program, because at the time it was really staffed just by Elizabeth Thompson and Joy Boyer. Joy -- Elizabeth had been there for several years already -- actually, both of them had already been there for at least a couple of years. But they needed another body, just generally to help with the growing, you know, budget, which was making it possible for them to fund more

and more grants. But also, more specifically, it was a time when it was becoming apparent that the institute was very quickly going to be moving from just thinking about issues connected with doing the basic genome sequence to doing -- very -- yeah, many sequences and looking for differences. So, you know, the -- all the kind of -- the mantra at the time was, you know, "All humans are 99.9 percent the same," but they were going to start looking at that little 0.1 percent difference, and they knew that that was going to generate a lot of ELSI issues. And so, the main reason that I was hired, at least initially, was to really focus on that part of the portfolio, to start developing a portfolio of research on ethical issues connected to genetic variation research and all the different kinds of issues that that would raise. Because the institute was very aware that that was sort of going to be its next area of focus.

At the time, it was interesting because it was always a part of extramural and it was -- I mean, the great thing about the ELSI program from the beginning is that we had that five percent set aside, you know. Legislatively, five percent of the budget had to be allocated to ELSI research, so we never had to fight for our five percent of the pie; it was always there. And that was really nice, because it gave us that sort of protected status so that we didn't have to complete for dollars or convince the people in the other parts of the extramural program that our research was worth supporting. I think some of them probably didn't really think it was initially, but they couldn't really fight with the fact that, by law, you know, five percent of the budget had to go to us. And so, some of it, you know, was maybe a begrudging acceptance of ELSI, but some of it, I think, even from the very beginning, there were at least a good number of people in the non-ELSI part of the extramural program that were always actually fairly supportive.

Well, it was really Elizabeth Thompson and me and Joy Boyer. It was really the three of us. Joy Boyer was technically a program analyst, not a program director, because she didn't have a PhD. But she was from the very beginning, you know, really coequal with us in terms of sort of the intellectual leadership of the program. And so, it was really the three of us together that really worked to set these priorities. Now, some of them had been set before I came there that Elizabeth and Joy had -- and, actually, Eric Young, who was the first director of the ELSI program -- had started with, you know, sort of the first vision. But then, by the time Elizabeth came, she had, I think, moved priorities a little bit more in the direction of clinical research. And so, I would say that when I came in, the main focus was still primarily clinical. Elizabeth had shepherded a couple of really good RFAs; one of them early on focused on carrier testing for cystic fibrosis. And then she had put together something called the Cancer Genetics Research Consortium, which was a -- that was a very, very nice group of early researchers who were looking at the ELSI issues connected with, you know, predispositional testing for cancer risk. It was interesting, though, because most of -- you know, in those days, the focus was really largely on single-gene disorders, you know, Mendelian conditions. And so, even with the cancer genetic consortium, which was very forward-looking, but it was mainly focused on the fact that, you know, they had recently found the BRCA genes for breast cancer. So, it was still very sort of single-gene focused, and a lot of the other work -- you know, cystic fibrosis also, you know, very single-gene focused. And a lot of the other ELSI research that was being supported was also focused on these much less complex conditions than what we're dealing with today. So, for example, Huntington's disease was also a model that was used, you know, for a lot of, you know, the autosomal stuff. And it was interesting in those early years, because I think that that focus, which made sense at the time because that's sort of where the science was -- but it did lead to

this sort of a sense for a number of years of this sort of genetic exceptionalism. There was a, you know, sort of sense that somehow genetic information is different and it needs special protections that, you know, other kinds of information don't need or don't need as much. And there was a lot of years spent, you know, sort of debating that. You know, is genetic information really different, or is it similar and we're just making a big to-do out of it because we happen to have five percent of our budget to focus on it, so we're making a big to-do out of it? And you know, to some extent, that issue still isn't completely resolved, but I do think that over time, as the science has moved and as now we know that, you know -- and more of the focus is on these common complex conditions and traits -- we've -- I think that the tendency to view genetic information as really different and as exceptional has waned quite a bit. But in those early days, that was very much sort of where we were at, which was a reflection of where the science was at.

Exactly, yeah. And so, there was -- in the early days, you know, there was this talk about, you know, genetics as your future diary -- yeah, a barcode, you know, as if somehow -- this sort of deterministic quality. And of course, if it really is so deterministic, you know, there is something to worry about with, you know, privacy and discrimination and all that. But I think we've come to realize that it's a lot -- you know, things are a lot mushier. And so, though, obviously, privacy and discrimination are still big issues, it's not so clear that they're really that different with respect to genetics than they are with anything else. And the behavioral genetics is a perfect example of that, where, you know, we now recognize that, you know, behavior is, you know, influenced by just -- everything. You know, hundreds of genes, a million different things in, you know, the environment. And so, it's -- you know, these things are complex.

Yeah. I would say in the early days it kind of broke down into two groups of people. There were various -- there were genetic counselors and also sort of nurses and social scientists. They were a lot of the people who were looking at the clinical issues, the cancer genetics kind of stuff. But then there were also from the very earliest days -- there were sort of philosophers, people who were sort of, you know, thinking ahead about the future of, you know, behavioral genetics and genetic enhancement and those kinds of more philosophical issues that, in some sense, you know, some people even thought it was being kind of science-fiction-y because they were sort of looking so far out into the future. And so, there was kind of -- in a way, there was sort of always these two groups, the people who were a little bit more clinically focused, who were a little bit more in the here-and-now and dealing with the actual current state of the science, and then there were the kind of the more philosophical types who were kind of always looking a little bit more into the crystal ball of the future and doing a lot of speculating. But to a certain extent, that was absolutely appropriate, because part of the mission of the ELSI program always was to anticipate the issues that, you know, were possibly going to arise in the future. And so, that's always been part of the mission; it still remains so today.

And I would say that we still see in ELSI research a combination of balance, and it shifts, you know. At different times, there's been more or less emphasis in one area or the other, but there's always been kind of the more practical kinds of here-and-now issues, you know, like -- you know, how do we -- you know, what kind of decision aids do we give people to help them make informed choices about, you know, testing or, you know, being sequenced on the one hand. And then, on the other hand, people looking at these questions about, you know, enhancement or -- you know, now, today we've got CRISPR-Cas or -- you know, and those kinds of things. So,

yeah.

Well, it varied. I mean, when I came on, as I said, you know, one of the things that I was hired to do was basically to do an RFA focused on ethical and legal and social issues related to genetic variation, because Francis already knew that he was about to launch, you know, a major genetic variation project, which eventually became known as the HapMap. But -- and so he knew -- he could foresee that there were going to be lots of issues on the horizon, so he very much directed that, that this needs to become a new priority. And so, I was brought on to address that priority, in addition to, you know, the other things that were already part of our agenda. So, you know, that was an example of something that was very much directed from the top. There were other things, too, that he very much felt that the portfolio was lacking in and wanted to see more. One of them was intellectual property. We -- in -- there were a number of years there where there was a sense -- and he was hearing from the broader community that, you know, you've got this ELSI program and they haven't really done anything on intellectual property. So, there was a lot of encouragement to do more in that area, and we did do more, although, as I recall, we did an RFA that really bombed [laughs]. It just -- you know, it just kind of -- we didn't get the applications to fund. And so that didn't really go anywhere. But on the other hand, it did encourage people to at least, you know, recognize that it was an area of interest, so eventually we got in investigator-initiated applications in that area. So, there were certainly areas that Francis and, you know, the other leadership within the institute were really pushing us to move into, but I think there were other areas where they were very much hands-off, you know, recognizing that, certainly in something like this, that you have to allow investigators, to a large extent, to kind of determine for themselves, you know, the areas that they see as being important areas on the horizon. Because I think there was always a little bit of a sense, you know -- there was always a bit of a tension with a program like the ELSI program that's situated, you know, within the agency that funds this underlying science. And there was always kind of that tension of, you know, how independent can you really be because -- you know, how much can you be allowed to fund -- people who are really going to question, you know, some of the fundamental premises of the science that you're funding? And so, there was always a bit of that tension. But I think that Francis recognized that you needed to allow some space for that, and he did allow that space. It -- so it often was more a question of the balance of the priorities and, you know, how much of our budget we should be devoting to that kind of stuff as opposed to the more pressing, immediate issues that he wanted answers to.

Well, truthfully, when I first came on I really didn't have a clue. This was not an area that I had ever really particularly been focused on, so I had to do a lot of, you know, sort of catch-up reading. And actually, there wasn't even all that much to catch up on, because there hadn't been a lot of research funded on these kinds of issues, but I quickly realized and came to recognize what the issues really were. And you know, a lot of it had to do with kind of the history of genetic variation research that had predated my coming there. There was a project called the Human Genome Diversity Project which was never really an official project; it was really kind of a loose conglomeration of various researchers who were interested in -- just in studying various, primarily indigenous populations, many of them small populations -- isolates -- you know, around the globe that were quickly disappearing. And you know, a lot of the motivation for that project was kind of an anthropological notion of, you know, we want to sort of, you know, get in there and study the genetics of these populations before they disappear.

And so, it was a project that was very controversial from the start. It engendered a lot of antipathy among a lot of the indigenous communities, certainly among Native American communities, in part because of, I think the history of eugenics, you know, that way predated the Human Genome Diversity Project. Some of that was absolutely, completely understandable where it came from. Some of it probably was misplaced, and some of it was, I think, a matter of miscommunication about some of the [coughs] -- excuse me -- the priorities and, you know, what the project was really about. [coughs] Excuse me, I'll just get some water here. So, in any case, there was this legacy from the Human Genome Diversity Project, and a sense from that project that -- the term "helicopter science" was sometimes used, you know, that they came in and they were grabbing samples from these communities and then leaving, never returning to let them know, you know, what came from the research. And it wasn't really healthful at all particularly, and so there were -- you know, there was a legacy there. And again, I think to some extent the criticisms of the Human Genome Project are overstated, and I think historically there's been a more nuanced view of that project and about the whole history of genetic variation research. But certainly, there were issues with it and we learned from that in doing the HapMap, and were determined not to make some of the same mistakes. But -- and you know -- and we certainly made our share of mistakes, too, in the HapMap project and in the other projects that followed. I think this is an area where I think everybody who does research learns from the mistakes of the people who did it before, because it's a very complex kind of research to do in a way that's really ethically sound, because you're dealing with -- inherently, you're dealing with people from -- with different cultural backgrounds and different -- and issues about race and ethnicity and, you know, ancestry and all of those kinds of issues, and the specter of eugenics, and all of that kind of stuff. That was, you know, part of what I had to very quickly get an education in. And we were really helped by the fact that when I first came in we -- before the HapMap project even began, we put out this RFA to solicit research on the ELSI issues connected with genetic variation research, investigator-initiated research, so it was unconnected to any particular project. But some of it was historical studies, you know, looking at the legacy of, you know, the diversity project and some of the other, you know, kinds of research that had been done in the area. We funded cultural anthropologists; we funded historians; we funded philosophers. And there was some really important work that came out of that that was really important to have in hand before we went into the HapMap project. One of the big things that we learned from that research was the importance of real precision in the way that you are going to label populations, because, you know, historically, I mean, it was kind of astonishing, you know, to see, you know, genetic researchers who otherwise would be very precise with everything that they did in the science, but somehow, when it came time to labeling a population, would think nothing of just calling them black, you know, or American Indian, as if there's no, you know, variation among people who happen to have the same sin color. And so, there was a lot of sophistication, I think, developed in those early years of study through that genetic variation consortium about what some of the pitfalls are. We were able to avoid some of those in the HapMap because we had done that foundational research.

Yes, there had been research. Morris Foster was an early proponent of this whole concept of community consultation or community engagement. Some of that grew out of the -- actually, the legal need for formal consultation with certain American Indian tribes or, you know, other groups around the world who had their own organized community structures.

But some of it was just a growing sense that any time you approach any kind of a community, however it may be defined, it's important to kind of understand the general notions of the group of people that you're going to be working with and collecting samples from to make sure that they understand what it is that you're proposing to do, and to kind of get their take on the whole thing, and to make it kind of a -- more of a bidirectional kind of thing so that you're just not coming in there and grabbing samples, but really making clear what the purpose of the research is and giving them a chance to object and say if they don't want to be part of it. And so, that was really the genesis of the community consultation, and you know, through that process, I mean, we made some decisions which at the time actually were -- and still probably do remain -- somewhat controversial about some populations not to include. For example, there was -- you know, we held a meeting with a number of representatives from the various American Indian tribes, had a lot of discussion about, you know, did they want to be a part of this project, or didn't they? There were good reasons to do it and some good reasons not to, and ultimately, they made the decision that, at least for that point in time, that they felt that, you know, they had other priorities. And we were able to, you know, respect that and didn't include their samples. Which, of course, raises its own set of ethical issues about representation and, you know, making sure that everybody is -- you know, that they're -- that you don't have only some groups represented in these important genetic resources and not others. And that's something we still struggle with today, that, you know, the resources that we do have are very imbalanced and incomplete, and they're -- you know, they're way -- we have a large overrepresentation of European ancestry. So, you know, it's a double-edged sword, but…

Yeah. Yeah, and that -- oh, you know, [laughs] it was so many years ago I can't remember all the, you know, back and forth. And that was a complicated dance of, you know, international politics, funding, you know, where the money was available. I mean, it largely came down to a lot of, frankly, compromises that had to be made between, you know, sort of the science and what was practical, what was feasible within the budget that we had at the time. And so, it -- you know, what we ended up with was -- essentially, we included the -- what's called the CEF samples, which are the set of samples that have been used for years, largely from people with European ancestry. These had been collected a number of years ago in Utah. And then we had a population of Yoruba from Nigeria who were included, and then two populations from East Asia, one Han Chinese population from Beijing and another Japanese population that was collected in Tokyo. How we came to those four -- there was a time, actually, when the project first began, before there was interest expressed by the Japanese funding agency, it was being really conceptualized purely as a project that we were going to do in the U.S. with, you know, sort of people with African ancestry living in the U.S. and people with ancestry from China in the U.S. And then, you know, as other funding agencies became involved, it basically expanded, was sort of Francis's idea, like "Let's make this a truly international population and go the countries where these people, you know, originated." And so, for the first phase of the HapMap, that's what we ended up with, was these four populations. We did, however, continue to collect these samples in the U.S. from some of these -- the other, you know, populations in the U.S., which became a part of a later phase of the HapMap, and those samples continue to be studied and used, you know, just like the ones in the -- that were part of the international HapMap project.

Yeah. Yeah, I mean, I think there were probably some people -- in fact, I remember this, that

there were people on the outside saying, "You know, you finished up the sequence. You know, declare it, you know, victory and close up shop," you know, basically. "You're done now, you know. There's no need for, you know, another big, you know, high-profile -- "project." Absolutely. Oh, people within the institute, very much. And -- yeah. [laughs] Yeah. No, I mean, a number of people. And then there were people who said, "Well, no, but we're not done yet, and there's a lot that we actually learned doing the sequence that we can apply to create other resources that are going to be equally if not more useful in many ways." Because, again, it gets back to that fact, you know, the original sequence was just intended to be kind of like some amalgamated human sequence. But I think, you know, we recognized that if we're ever going to actually be able to use the sequence to start to look at, you know, what makes some people more than others susceptible to certain diseases, you're going to have to start looking at that part of the sequence that differs. And so, I think it was felt, and I think this was certainly Francis' feeling, that the genome institute, you know, with kind of what we had learned from doing the sequence -- we really knew how to create large resources. And so, that's really what, to a large extent, the genome institute has become over the years, creating these large resources that then can be mined and used by people in the other NIH institutes who are studying particular diseases. But we create the resources; they then use them to study their diseases and come up with their -- you know, the discoveries about their diseases. So -- but it certainly was a point of contention about whether this was something that really justified a whole new big project or something that was just, you know, trying to find something else to do to keep ourselves sort of in the, you know, limelight.

There was about four years there, I would say, from about 2001 to 2005, where it -- I -- you know, 100 percent of time, but even more than that. I mean, it was -- I mean, we hardly slept. Lisa Brooks and I -- I mean, Lisa Brooks was doing the, you know, basic science part of the project and I was doing the ELSI and community consultation part of the project, and it really took up a huge amount of time. It became an incredibly complex project, just between -- just trying to, you know, handle these community consultations with all these different populations. And then, just trying to sort of navigate the international politics of it all. I mean, it was really complicated, and a rollercoaster ride, but it was very interesting and we learned a lot from it.

Well, I never really had any doubt that it would work. And I had no doubt that we would succeed in, you know -- eventually, the -- we would have our HapMap. And I also had no doubt, really, that it would be a useful resource. Never had a doubt. I do think that there was some sense among some people, I think, early on that the HapMap was going to be a more -- it was going to be a simpler route, you know, from creating the HapMap to, you know, doing the GWAS studies and finding the genes associated with these various diseases. And I think it was for some people kind of a rude awakening that "Oh, no, it's going to be a lot more complicated than that." But I -- that never was really a surprise to me, and I don't think there's any question, I mean, even years later, that that resource has just been incredibly valuable and has been a foundational resource for the other resources that have come since then. So I was never really a doubter, but certainly there were people who were.

I think there were people who did, absolutely, yeah. Yeah. But it wasn't simple. But I think in the very complexity a lot was learned. A lot still is being learned. You know, the common variant, you know, common disease hypothesis, you know, didn't bear out in the way that I think

some people thought it would, but what we did learn was, you know, just sort of what are these patterns of variation and how they do relate to disease. And it's been, I think, incredibly important.

She was, you know, really the person who kind of kept all the balls in the air. You know, just keeping the science moving, keeping everybody accountable, you know, helping to navigate the politics, you know, the international politics of it all. She was just very hands-on and extremely calm, you know. It didn't matter what happened; Lisa never got frazzled, which was really great because there were lots of times where it was easy to get frazzled, and Lisa never did. Of course, Francis was also very hands-on, too. And that was one of the things that actually made the project really interesting to work on, because both Lisa and I worked so closely with Francis, because he was really very, very closely involved with all that. And it was just great to see sort of how he managed a project, and kind of to watch him apply the lessons that he had learned from managing the sequence and, you know, carry them over into the HapMap.

You know, I mean, I just think that he learned sort of how to -- knowing how much to kind of take control and be a little dictatorial, and how much to, you know, sort of -- we would have these, you know, weekly -- I think they were weekly -- calls and how much, you know, to sort of -- to allow the discussion -- you know, to sort of allow sort of a consensus to emerge. He's just really good at that, at sort of knowing how to move things along and when you just have to make decisions and just say, "This is going to be the way it is," but without sounding too dictatorial and -- but when to actually kind of -- to listen. So, he was very good at that. The one thing that he was very bad [laughs] which, you know, caused constant frustration for us is just that, you know, this is Francis. It's -- he's -- everything is always -- you know, everything -- he's always in a rush because, you know, the science has got to get done. He wants it done like tomorrow because he -- you know, and then he wants to move on to the next thing, because he's just -- you know, he's very visionary that way. And so, it was sometimes exhausting just working with him because he was always pushing, pushing, pushing, you know, faster, faster, and that was frustrating. But ultimately, you know, that's what helped to get the project done. And it did move the science along, so I don't mean it as a criticism. But it's just -- it's -- when you work with Francis you just learn that everything is on an accelerated timeline. It just is.

Oh, there were lots of, you know, 3:00 a.m. emails and -- yeah, and emails that I would send at 3:00 a.m. that would be answered by Francis at 3:10. And that was also one of the amazing things about Francis, is that, as busy as he was, he always answered emails, and he always answered them in complete sentences. That amazed me. You know, like other people have typos and, you know -- Francis -- I mean, it's always just amazing that he was so responsive in that way, and it's, I think, part of why he's so effective.

Yeah, I mean, I think the big thing was just the complexities of working internationally with -- and also in a funny situation where part of the work was being funded by other countries like Japan and China, but part was being funded by us. And from the ELSI standpoint, sort of trying to ensure that there was a sort of a baseline, you know, minimal set of sort of ethical standards that were -- could be agreed upon that would, you know, sort of comply with the international ethical guidelines that were out there. But at the same time, being able to sort of accommodate these local cultural concerns which, you know, of course were, you know -- none of us were

experts in these, you know, the local kinds of concerns that would come up. And so, sort of how you sort of navigate that, you know, trying to ensure some level of consistency and to basically say we're having some minimal standards, but at the -- some minimal common standards that we're all going to meet, but at the same time, you know, sort of providing some room for the local sort of cultural climate. And it's -- it was very tricky, because even, you know, the international ethical guidelines that exist out there -- you know, most of them reflect a very Western bias and we certainly ran across that. And so, it was tricky, you know, sort of trying to navigate that and sort of recognize that there is Western bias written in, even into these things that we think of as being international. And -- so that was tricky.

No, I mean, this -- and this is where my memory gets a little hazy. But it -- but I think it was just simply a matter of, you know, we had -- by that time, we had, you know, a number of samples that we collected here in the U.S. that -- from many interesting populations that we wanted to genotype and actually add them to the HapMap resource. They weren't a part of the international project, but we wanted them to be part of the general resource that could be available and used for future studies. And so, that was really the motivation for that part of the project. And in truth, I wasn't really that involved in that part of the project, because the samples had already been collected. The genotyping -- you know, the protocols for doing that had already been -- you know, that wasn't part of my bailiwick, and so I wasn't really that involved in that actual part of the project. I did get more involved again, then, obviously, when Thousand Genomes began because there then again it was a question of, you know, making decisions about which populations to include, which to not include, and how to, again, make sure that these samples were going to be collected in an ethically appropriate way. And you know, that project in many ways was more complex because we're talking about even more populations from more different parts of the world. But you know, we were able to sort of build on what we had learned in the HapMap. And we did not have nearly the same level of intensive community consultation and engagement that -- for Thousand Genomes as we did for HapMap. It just wasn't even a possibility, just because of the number of populations involved, and also the fact that most of those sample collections were not -- we weren't funding those sample collections, so we certainly couldn't impose upon them, you know, exactly how they were going to, you know, collect the samples. So, that was much more -- there was a little bit more locally distributed -- but we still -- you know, again, we had minimal standards that had to be adhered to. We had a, you know, common template that we used for the consent form and certain minimal things. And just as with the HapMap project, we set up a sort of a community advisory body for each of those populations. And to this day, we continue to provide quarterly reports to, you know -- for all the communities that provided samples, for all the HapMap populations, and all the Thousand Genomes populations, so that people who are interested and want to see how their samples are being used have access to that information and also have some information just about how the resources themselves are being used and what kinds of discoveries are being made.

Oh, Charles was incredibly important, and Charles was very pivotal in that he felt very strongly from the beginning that if we're going to include, you know, African samples, they need to be collected in Africa, and he was very, very vocal about that. And I think he was absolutely right about that. And he had, you know, obviously done a lot of work in Africa; he had very good collaborators there. Clarence Adebamowo who was his -- the local collaborator who worked with him on the Yoruba sample collections, a great guy who's actually -- who really, starting with the

HapMap, really has developed a career as a real, you know, African ELSI bioethics person. I mean, he has really helped to develop a whole research infrastructure there for bioethics in Nigeria, and none of that would have happened without Charles and without, you know, his leadership and in connecting Clarence into the project and connecting that Yoruba community. And then, also, he was pivotal in helping us to connect to some of the communities that were part of the Thousand Genomes project as well. So, Charles was great, and Charles was also -- you know, had -- having done a lot of work in Africa, he had done a lot of community engagement there. He knew, really, how to work in those communities and it was great, and we learned a lot from Charles in those communities.

A great anecdote that I recall from the HapMap project was, you know, we think, you know, that, you know, in a culture where, you know, it's pretty much a patriarchal culture, and we were concerned that, you know, women not being, you know, felt pressured to donate samples because their husbands wanted to donate or, you know, wanted the -- you know, were collecting actually trios, parent-child trios. We wanted to make sure that, you know, women were, you know, informed consent by our sort of Western notions of informed consent. And I remember that, you know, one of the things that we suggested to them, that, you know, if the women would feel more comfortable, that they could go into the room and we would give them a Band-Aid that they could put on their arm so that if they really didn't want to donate we could still give them a Band-Aid so that they -- you know, their husbands could think that they donated and that way, you know, they would be respecting their wishes, but at the same time, not, you know, making them have to come out and tell their husbands, "No, I didn't want to give a sample," and then their husbands would be upset. And I remember the women looked at us and said, "Well, why would we want to do that? We want to do what our husbands want us to do," you know. And so, again, this great idea that we thought we had about, you know, the Band-Aid on the arm as the great thing that was going to protect their autonomy interests -- you know, autonomy wasn't exactly at the top of their list of things that were important to them. So, things like that that, you know, you learn by doing this kind of research that, you know, you think you know best, and you don't know best very often.

Well, of course, after HapMap was Thousand Genomes, but even then, my role was slightly reduced from what my role had been during the HapMap. And then, really, then, you know, I became much more involved in all of the other projects that, you know, NHGRI is involved in that has any kind of an ELSI component. And I became involved in a lot of the, you know, sort of the trans-NIH kind of stuff. So, you know -- I mean, the eMERGE project. We had a piece in that. The -- I became actually very involved for -- I don't know, it was probably actually shortly after Thousand Genomes -- in the Human Microbiome project, which was actually a trans-NIH project, not just an NHGRI project. Yeah -- or, yes, common fund. But because NHGRI had kind of an outsized role in it, we managed to get a built-in ELSI component into that project, too. And so, we -- I put together an RFA on ethical issues in human microbiome research, and that was very interesting. And that was very interesting because it was working with, you know, microbiome researchers who -- most of whom had, you know, never heard of anything called ELSI, and this ethics stuff was completely new to them. But it was amazing how receptive they were to actually thinking about the kinds of issues that -- you know, some of it was just day-to-day issues that came up in the research in terms of how they would collect the samples and that sort of thing. But some of it also was looking at these broader, sort of philosophical issues like,

you know, what are the sort of ethical issues connected with microbiome research? And you know, how are we going to communicate results if, you know, the research shows or suggests that there's a difference or, you know, a statistical difference in the way the microbiome looks in people from one racial or ethnic group than another? Things -- you know, notions of, you know, contagion and disease and those kinds of things all raised really interesting ELSI issues that, you know, we funded research on, and the microbiome researchers were really interested in being part of that. So, I did a lot with that, did a lot with the, you know, NIH data-sharing policies as they were being developed over years, and they're still evolving, obviously, today. And then the big issue, the big project that I became involved with -- oh, goodness, I don't even remember what year now; probably six years ago -- was the clinical sequencing research -- clinical sequencing exploratory research, or CSER project which was a, you know, very large project, and all of the sites that competed successfully were required to have a specific component of their grant that would be focused on ELSI research and ELSI issues. And so, there's a lot of work that I've done over the years with clinical sequencing. Probably the biggest set of issues there has had to do with all these questions around return of results and incidental findings. As you know, there's, you know, a huge amount of debate over the years, but we fund a lot of research on that because when we first started the project and we were going to, you know, be sequencing all these people, we knew that inevitably we were going to be generating all these incidental findings. And no one really knew what to do with them. You know, what do you do? You've consented people, you know, that you're going to look for, you know, an answer to their whatever it is, particular -- whether it's a, you know, neurodevelopmental disorder, you know, whatever, or a cancer. And you know, you may or may not find what you're looking for, but you're inevitably going to find these incidental findings. And in the beginning, no one really knew what to do with that information. Would people freak out, you know, if you were going to tell them something that, you know, they weren't expecting to hear, and now they're going to -- you're going to, you know, worry them about something? And what would be the consequences? Or would people be, you know, upset if you withheld the information? And so, we funded a lot of research on that over the last several years and we're still funding research on that, because the answers aren't -- still aren't completely clear, although what we have learned is that I think that some of the initial concerns that people would be, you know, freaking out and going out and committing suicide because they found out that they had a gene that was something going to perhaps predispose them to, you know, disease X or Y -- a lot of those fears, I think, were overblown. And so, I think there's been, you know, a greater tendency to want to give back that kind of information, particularly because people say that they want it. But of course, that raises its own set of issues, you know, both practical issues and ELSI issues. And so, that's -- those issues we're really continuing to grapple with and I think we will for some time into the future.

Well, actually, NCI does now have a fledgling -- but it's not really a program, but there's – Charlisse Caga-anan, who was actually one of our grantees previously, now is over at the NCI, who's basically developing, you know, an ELSI portfolio. Now, relative to the total budget of the NCI, you know, the portion of their budget that goes into ELSI research is very, very tiny because, you know, they're huge. And so, it's certainly not five percent of their budget. It's just an infinitesimal amount. But it does exist there, and there are certainly people at NCI who are recognizing the value of this, I think in part because, you know, they're encountering these issues now, you know, with sequencing for cancer. And so, you know, they've begun to fund more of this. Certainly, child health has always been a pretty good partner, you know, historically,

because so many of these genetic issues do, you know, come up in childhood. I mean, certainly newborn screening -- they're a part of the whole newborn screening initiative now, which has a dedicated ELSI component, and they've funded -- you know, we've co-funded with them a fair amount of other ELSI research that, you know, as long it's focusing on issues relating to pediatrics. So, I would say NCI and child health have been fairly good partners, but again, neither of them, you know, is like us in that they have a set-aside of, you know, five percent, or any percent, that they devote to this kind of research. So -- but there -- and NIEHS historically also has had some interest in this area and has occasionally co-funded stuff with them, as have a number of other institutes, but mostly just kind of sporadically. And so, it really has been a problem trying to sort of get other institutes to recognize that, you know, there's a role for them here, and especially now as, you know, so much more of this is moving in to the clinic and these issues are coming up in the context of specific diseases, not just sort of in the abstract anymore. And so, our feeling is that, you know, some of this we should be able to sort of hand off to those institutes and they should be stepping up to the plate. It hasn't happened as quickly as we'd like to see, especially with most other institutes. So, that does remain an issue. And again, I go back to the fact that I think that, unless you have some kind of a mandated set-aside, it's very, very hard sometimes in these other institutes to compete for dollars. Even if an application has a good score, it's seen as being something that's, you know, perhaps less important than funding the basic science. And there are certainly people in other institutes who even see it as being beyond the purview of the NIH, you know, that that's just -- we don't fund ethics or we don't fund legal stuff. So, that attitude is still there and I think it's going to probably be there for a fair amount of time. I think, actually, one of the bigger issues is not so much -- I think that there's a dearth of interest among -- you know, in getting the ELSI research connected to genetics and genomics funded, but there's also these bioethical issues that have nothing to do with genetics but that arise in all these other areas of medicine that are just barely getting looked at at all. And I think that's almost where there's a bigger gap than there is with the, you know, genetic-specific kind of ethical issues. But -- yeah.

You know, right to die, those kinds of issues that, you know, come up with all sorts of different diseases. And no one's really looking at that. Nursing Institute does some of that, but you know, those kinds of questions -- informed consent -- there are all kinds of informed consent issues that come up with respect to all sorts of treatments, certainly mental health treatments. Don't necessarily have anything to do with genetics, but you know, dealing with vulnerable populations and how do you get meaningful informed consent. They're doing very little of that. They do some, but I think there's a real gap. So, I mean, there's just all sorts of other examples. There is a trans-NIH group called the CCBRT, which -- oh, goodness, I can't even remember what the acronym stands for -- yeah, but it stands for something about bioethics research and training. That really is trying to look across NIH at, you know, all the different portfolios of the institutes, at what's happening in terms of bioethics to get a handle on it and to advocate for more of this funding. But you know, it's a slow process.

Well, it's -- I mean, you know, that's the thing. ELSI really just is the acronym that describes our research program, and in a narrow sense, it's nothing more than that. But in fact, it's come to mean something broader. And in fact, it's come to mean something even beyond genetics and genomics. It's just come to mean this whole -- and even just to call it bioethics is too narrow because it's not just bioethics, it's ethics, it's law, it's all the social sciences. It's history. It's --

and it's clinical medicine and basic science. It's that whole transdisciplinary way of looking at science and really putting together people from these various disciplines who approach these issues in very different ways, but to put their heads together to try to come up with the most sophisticated and nuanced ways of addressing these really hard issues, most of which have no clear answer. So, I think that's really what it is. It's a pretty ambitious enterprise [laughs] to say the least.

The one thing I would add is just -- because I didn't really get a chance to talk about, you know, our training program, which I won't go into the details of except to say that that's a big part of what we fund, too, is, you know, to really fund training for sort of the next generation of people to do this kind of research. And we've had some spectacularly good ELSI trainees, especially in recent years. And I think that, you know, as these new issues are coming down the pike, I think, you know, they're really the future, and I'm so impressed with, you know, what I see there in terms of creativity and ways of looking at these issues in really transdisciplinary ways. So, I think that -- you know, that gives me a lot of, you know, positive feeling about where this field is going in the future, even though there are days where I feel negative because I feel like, you know, there needs to be more funding and, you know, more people need to be doing this. But there's good people on the horizon.