Bob Cook Deegan
So what I would like to start up with today is, "What next?" What is the National Human Genome Research Institute after the Human Genome Project is completed? And, how did you think about the transition from doing a project, to next things that are important to do?

Francis Collins:
Well, having the draft announced in 2000 was a milestone, but maybe scientifically, more importantly having the publication on the draft in February 2001. It was pretty clear at that point, we are going to finish this. We're not going to leave it as a draft. That would be unfortunate.

As with most things, the last five percent is about as much work as the first 95 percent and that was certainly the case. So there was an awful lot of work to do there for the next two years, until 2003 when we basically said, "Okay. We have a complete human genome." Admitting at the same time there were bits and pieces of it, like centromeres, that had not been completed and still have not because of the nasty nature of those DNA sequences preventing you from being able to assemble them. But just the same, it was a moment.

On April 14, 2003 we had an event in the Library of Congress. We said, "Okay. We've really, really gotten to all of the goals that were put forward for the Human Genome Project 13 years ago." So, it wasn't just that we had the first reference human genome sequence. We've also accomplished all the other things that were part of that effort as laid out by the National Academy original blueprint. So, it was really a moment. And you might say, "Well, then we should all fold up and go home." But obviously, that would have been kind of leaving the good part unattended to. Because this was laying out a foundation and I had to build on it.

And knowing that was coming, we had spent something like 18 months really working hard on sampling all the bright brains out there about what would be the next appropriate goals for the field of genomics, not just genome sequencing. And where should we place the resources and place our bets in terms of what the Genome Institute could do to keep that momentum going, or even accelerated? And that was a bunch of workshops and one very large meeting at the beginning, and a lot of workshops and another large meeting at the end that sort of pulled this together and ultimately a document that laid out what the plan was going to be, published in *Nature*. So, we made it very clear -- here's what we think is next -- and that was published simultaneously with saying, "We have now completed the goals of the project."

And it needed, of course, a visual [laughs] and I was struggling with what that should be, and went to Borders bookstore to sort of look through books of various kinds of images, and happened across a book of Falling Water, Frank Lloyd Wright's most iconic structure. And that was like, "Okay. We can do something with this." And so there it was as figure one in that paper, describing the future of this building which had three levels but it also had cross-cutting elements. Maybe it was helpful. At least, I used it for the next two or three years to kind of explain the various areas that we were trying to nurture.

And out of that, I mean, came a lot of what came next, although some of it already started. I mean, we knew that having a reference human genome was nice, but the .1 percent of variability and the well-behaved part of the genome was intensely interesting, and we should start looking at variation

and we had already started doing that, well before 2003. But HapMap, as one real flagship next effort was clearly a part of where to go next.

And we wanted to understand function. And, that's the motivation behind putting together the idea of ENCODE, the encyclopedia of DNA elements and how we could -- by building on lots of laboratories that had lots of capabilities in a challenging, cooperative-agreement kind of mode -- begin to understand what were the parts list of, what was the parts list of the genome and how do those parts make sense, in terms of regulation.

There were other really important parts that related to ethical, legal and social issues. We had not solved any of those as definitively as we would like, obviously, especially genetic discrimination. There were lots of issues about advancing technology and not wanting to stop with DNA sequencing abilities we had in 2003 because we knew one genome for $400 million was not going to be a good long-term solution. So, all the more reason to put effort into dropping the cost, increasing the speed while not sacrificing the accuracy. All of the things that really played out beautifully, then, over the next 10 years and continued to, in terms of making sequencing ever more accessible and affordable.

Bob Cook-Deegan
So Francis, the politics of this -- so one way of taking that is you've gone from having a difficult problem of getting a whole bunch of people to work in concert for this incredibly big, international, huge goal and a huge public event for announcing success. And now, you've got a whole series of projects, and an institution that is driving science in genomics and your role as the NIH director sounds like it changes a little bit from trying to get to the goal line to -- and being the quarterback -- to trying to figure out four or five different games that are going on simultaneously. Is that a fair characterization?

Francis Collins:
In some ways, yes, because certainly something like ENCODE had a very different set of ideas and needs as far as pulling together a collaborative effort to look at the functional parts of the genome. HapMap, on the other hand, had a lot of the same flavor as the sequencing of the genome. It was international. It required a lot of coordination and Friday morning phone calls. It needed a field general, and once again, that was me, with lots of help from colleagues and other places, especially the U.K. But that had many countries involved and everybody had to agree to certain standards about quality and timetables and data release and all that.

So, HapMap, in many ways, was sort of the natural follow on and it was also sort of natural building on what had worked, in terms of how to make such a collaborative effort successful. So, that was pretty familiar territory, also pretty exhausting. And we had some different players in HapMap than we had had in the sequencing, which made it interesting because some of them hadn't had the experience of the sequencing project and were maybe not quite sure why they should give up their autonomy to be part of something of this sort. But --

Bob Cook-Deegan

So, Eric, you had a question that --

Eric Green:
Well, no, a comment I was going to make, which I think is relevant. I think an inflection point of the institute took place slightly before. And then in 2003, I think a lot had to do organizationally, due to the following reasons that, especially the leadership team and that 2003 plan came together in a slightly different way because of the differing core leadership group. You know, 2002-ish was about the time that Elke Jordan retired. Jeff Trent left as a scientific director. And that gave opportunities for a bit of shuffling. Francis appointed me the intramural director, the scientific director. Mark Guyer became the extramural director, and then Alan Guttmacher became the deputy director.

Francis Collins:
Exactly. The three G's.

Eric Green:
Exactly, affectionately referred to the three G's. And what I think was important was that 2003 vision that was published in *Nature* the day the Genome Project ended, and that 18 month or so process that Francis described, was very much of a committee effort. He really delegated to us a lot of responsibility for seeing this planning process go on, which really made it a trans-institute plan in process because intramural was as involved as extramural. And having Alan as the deputy, thinking about issues that complimented nicely what Mark Geyer and I could bring to it.

And so that document was effectually sort of the three G's plus FC was sort of the internal abbreviation for it.

Francis Collins:
Exactly.

Eric Green:
And I also think then leading on beyond that, I think Francis turned to not only the three G's, but lots of other good leaders within the institute to really help him more on individual projects. Mark Guyer and I went off and really helped, I think, develop some of the early blueprint for ENCODE. Alan certainly went off and helped on some specific areas. I think it was a more distributed effort, which gave him the opportunity where to decide where to spend more of his time, knowing that some of the other trajectories were taken good care of.

Bob Cook-Deegan:
Let me stay on that for just a minute because I would like to sketch out the signature of the National Human Genome Research Institute. What is distinctive about it relative to the other critters here in the NIH forest? It seems like there is an element of planning and anticipating where the science is going and systematic staff work. The politics, the leadership. Talk a little bit about top-down versus bottom-up science and what's the distinctive role of this particular institute compared to its brethren here.

Francis Collins:
No, it's a good question because certainly by this point, every institute is investing in genomics, one way or another. The technology has gotten distributed, not necessarily at scale the way it was in our large-scale sequencing centers but certainly many labs were taking a lot of advantage of the success of the Genome Project and that was good. What was the unique niche then for NHGRI? It was about this time, I think the IOM came out with their big description of what should happen to NIH which had a number of recommendations that might be considered, none of which have happened. In terms of shrinking the number of institutes and maybe NHGRI ought to sort of wander back into NIGMS and be absorbed in that space. Obviously, that didn't happen.

Though, it was crucial that NHGRI continued to serve, and to serve, they had to have some unique kind of role. And, I think that the unique role was genome science at scale, because other parts of NIH were really not prepared to do that. Now, that doesn't mean that it's all top-down. It means you want to induce very bottom-up technology that will improve the scale. And so getting, for instance, DNA sequencing to go faster, better, cheaper. I wouldn't say that was top-down. There is a lot of really incredible creativity going on in academia and in small businesses that Jeff Schloss brilliantly nurtured along. Look where that's gotten us.

But some of these were production projects, to produce community resources that should follow Bermuda Rules and therefore be immediately accessible. And you don't see those happen unless there is an organizing force. And that was, sort of, one of our visions of what NHGRI could continue to do, whether it was for ENCODE, whether it was for HapMap, how -- whether it was ultimately for Cancer Genome Atlas only a couple -- three years later. Whether it was the Knockout Mouse project, which was also very much something that got pushed forward from the Genome Institute.

Or, even whether it was -- and this was maybe the furthest departure from what had been our sweet spot -- the establishment of the Molecular Libraries Program as a means of trying to put into the hands of academic investigators High Throughput Screening capabilities for small molecules so that they could, in fact, go from diagnosing to thinking about treatment. And that was a personal strong priority for me, is to make sure that that opportunity didn't get missed.

And this came along at the point where [NIH Director] Elias Zerhouni had started something called the Roadmap, to try to find ways for funds to be collected that would not necessarily get spent by any single institute on a project but would, could benefit everybody. That was a timely -- that he had that vision that certainly turned out to be a way of extending the Genome Institute's ability to influence some of these game-changing projects that were large-scale, expensive, and beyond our own little budget.

Eric Green:
I mean, we had many opportunities, after 2003, and even more recently, to become more normal, relative, like all the other institutes and centers. I think there's a certain cultural flavor of the institute, I think an expertise-level at this, to be pioneers in the way the science is done. Now, that is a model for doing science. I don't think we've ever said it's the only model and is probably an unusual and rare one. I don't think every institute should be like us by any means.

But, we clearly did something very different in the Genome Project and the projects that -- the genomics projects that immediately followed the end of the Genome Project and they continued to receive, you know, good feedback about their importance. I think what they produced was valuable. And I think that the way we led them was key to their success and also proved to be an effective way of leading some types of science.

Now what does that get you, by the way, is it gets you more work because what it means is that when you're that rare institute that is capable of leading these efforts, and then other opportunities come up, common fund examples that Francis just gave are good ones. You're asked to take on a lot of that and carry a lot of the water because you're good at it. And that's fine. I mean, we embrace it and we prepare for it and we are as much to blame as anyone because we propose ideas that are bigger than our budget but are well within our intellectual capabilities and our leadership capabilities. And then when these ideas actually get approved, that means we have to actually do something.

Bob Cook-Deegan:
Do Something

Francis Collins:
Do something and find the-

Eric Green:
That's right. So, I mean, we end up being the over-achievers, I think in many ways, of the corporate level because of the proven track records of leading these large projects effectively.

Bob Cook-Deegan
So, a lot of this involves high-tech, whiz-bang instrumentation and data and computation. That's part of the signature. One other thing, though, and we talked about it in the last interview briefly, but I didn't talk about one aspect -- I didn't ask the appropriate questions about one part of it that I think is really worth clarifying: DNA sequencing, the core technology. You get this reference sequence. All over. You don't need to do anything more with technology, right? You've got your reference sequence. Well, no. This institute was heavily involved in almost a DARPA-like -- I mean, I think people would say, "Without Jeff Schloss, the world would have been a different place."

Francis Collins:
That's true.

Bob Cook-Deegan:
And there was leadership, anticipation, and that's kind of a -- you can't force that kind of technological innovation to happen from the top. You can provide the resources that enable it and the vision that feeds it when it's about to make a breakthrough. So, how do you guys think about

that? That's a different style of thing? And what were the -- there must have been some explicit thought about what you were doing to push DNA sequencing technology per se?

Francis Collins:
There was. And as early as 2003, we started talking about this mythical goal of the $1,000 genome. And it helps, I think, to lay out a goal that seems almost impossible to achieve to get people electrified by what that would mean if you could do that. So, that was part of it. Making it clear that we are not satisfied with where we were. Not by any means. We've got orders of magnitude that need to be crossed to get to where we want to be. And there's no reason not to get there. So let's be creative and let's put a lot of money into the technology development to encourage wacky ideas. If they have any chance of success, we're going to lay this out in a DARPA-like fashion that we expect failure to be extremely common as long as there is an occasional success, we consider this is money well-spent.

Another thing we did, and should have mentioned this already, is by making big investments in comparative genomics -- okay, we've got the human, but now we've got all these other species that we want to look at. And we want those to be high-quality genomes so that we can really do, as Eric Lander liked to say, look in evolution's lab notebook and see how every nucleotide has been affected by evolutionary forces.

That presented the concept of a huge market for sequencing machines, because we were therefore talking about many, many, many genomes of different species. And we were going on with HapMap, which you're not going to find variation unless you do sequencing, so we were creating a demand by making it clear that NHGRI was going to be spending a significant fraction of that half-a-billion-dollar budget paying for sequence and therefore anybody who has an idea about how to build machines that are a little bit more competitive than what's out there, they're going to find a pretty receptive market.

So all of the pieces, I think, were in place. And I think it's fair to say, at that point, maybe the government was the main driver of the technology advances. These days, as this has become more and more something that private sector themselves want and invest in, I think that momentum is gone to the point of being sustainable even if we [NIH] weren't making such a big push but our push is still awfully important.

Bob Cook-Deegan:
What's kind of the biggest surprise of where that's taken you? This ubiquitous, relatively low-cost sequencing technology. Stuff that you just didn't see happening, that wasn't part of your five-year plan or 10-year plan, or whatever?

Eric Green:
Microbiome would be one of the things that I would immediately list. And the speed with which microbiome research not only became an entity and a recognized and respected field of study but

seeing it happen so fast that it distributed so effectively across the NIH, the different institutes that you almost don't even need a centralized effort. We did the human microbiome project and now we're winding that down and it could be wound down because it was so clear that it was getting taken up by all of the individual entities. I mean, that happened much faster than I ever anticipated. That's one example.

Francis Collins:
I would agree. Cancer -- I remember having a conversation with our sequencing center scientific advisors. I don't know. Was it 2002? It was probably around that time. And, proposing "Well maybe if we can drive the cost of sequencing down we could start actually sequencing individual cancers and finding out what's driving them." And, at that point, Janet Rowley was one of our advisors and she was like, "That'll never work. You won't be able to make any sense out of it. There'll be all this noise from -- because cancer cells are mutating all the time."

And she was strongly opposed, which was pretty interesting. It took me back a bit. She came around, obviously, as we began to figure out how you do this. But yeah, one cancer cell sequence was going to be impossible to interpret. But if you had 20,000 of them, you could start to figure out what the signal was and what the noise was. And that's pretty amazing that we got there in the space of, you know, maybe five or six years after having that first human genome. We were deep into cancer.

Bob Cook-Deegan
So, one other thing that happens when you've got this reference sequence and you've got this signature of high-tech, whiz-bang, data-intensive science -- that's your style. Other parts of NIH (and other parts of the world and the other parts of the research apparatus) are beginning to see the value in what's emerged from this huge project and are beginning to want to play in that sandbox. That changes the role of this institute because it means there's a connection to all those other pieces. What does that feel like? Presumably, that transition's beginning to happen, even before the reference sequence is announced, but certainly after that?

Francis Collins:
I think it's been mostly a good thing as long as everybody's playing by the same rules about data quality and data access. I mean, take the Thousand Genomes Program, which has been obviously a huge contribution to understanding variation at the most detailed level. I think it's fair to say the push for that came a little more from the U.K. than it did from the U.S. The initial vision of this [came] particularly from Richard Durbin. And obviously, a lot of organization that went along with this effort that we were a big part of. But that seemed okay to me. That we don't have to drive every part of this. I'm sure we're going to talk about BGI here in a second because here's a remarkable center in Shenzhen that, at least for a while, had the largest sequencing capacity in the world. I'm not sure they do because they haven't kept up with the newest machines.

But, was that a threatening thing? It was to some people, I suppose. And it certainly was a surprise to people who thought that the U.S. would remain dominant for centuries to come. It wasn't that hard with energy and some funds for BGI to jump out there and create an amazing center with

amazing talent. Again, I never felt like that was such a threatening outcome as long as they're playing fair.

Eric Green:
I think the issue of NHGRI's relevance relative to the rest of NIH as genomics spreads across the NIH really became important to consider; the talent of Francis' directorship and in particular when I became the director. In fact, immediately when I became the director, we tried to do portfolio analyses to get a handle on "how much money are other institutes spending in genomics?" And those are hard data to come by: exactly what do you define as genomics? But it became pretty clear that by the time I was the director of the institute that there was more money, far more money being associated with genomics research and being pursued by other institutes compared to us. We were the minority genomics funders.

And that does make you pay attention to define your relevance. You don't want to be doing what everybody else is doing. That becomes a fun challenge. I don't think that becomes a threatening challenge. I never took it as a threat. But I do think that the 2011 strategic plan, which was the first one that we finished on my watch. The planning process started on the tail-end of Francis's watch. I think the 2011 plan, more than any other plan, clearly laid out a vision for what genomics needed to be, but also completely acknowledged that this was a vision that all of the biomedical research enterprise should be embracing. And that, within it, NHGRI would clearly pursue some things harder than others. But we would do everything we could to stay at the front, pioneering because that's always been our strength.

Bob Cook-Deegan
So Francis, what do you think, having been director of this institute had to do with your becoming the director of NIH? And then both of you, please talk about this transition because you're now the former director of this institute but you're the top gun at NIH and Eric becomes the director of NHGRI.

Francis Collins:
Well, I would not say that becoming director of NIH was part of my life plan at all. It's not like this was like "Okay, I need to step out of this one in order to be asked to do that one." By the time it got to 2008, I'd been in this job for 15 years, leading the Genome Institute. It had been a great ride. A lot of really cool things continued to happen. But I was getting restless and feeling like I probably have something else that I might want to do, but I don't know quite what it is. I really wanted to write a book about personalized medicine and couldn't do that in my government job, because it would be an overlap with my official duties. And I was just restless and ready to try something else. So, I went to [NIH Director Elias] Zerhouni and told him I was ready to ride off. He tried very hard to talk me out of it, shortly before he quit himself, by the way.

[laughter]

Which was interesting. And then in August 2008, that was sort of -- okay. I'm walking out, as we said, into the white space, not knowing what I was walking into, because I had no other job

lined up. And I did not know that that would result ultimately in just about exactly a year being called back in a different role, but so it went. I was, frankly, quite excited about the prospect of Barack Obama as a president who cared about science. So I worked on the Science Committee for his campaign. And then once he was elected, I worked on the transition team with Harold Varmus to be sure that everything was ready for inauguration on January 20th. And I don't remember much about Thanksgiving and Christmas in 2008 because it completely consumed by those transition activities.

But then inauguration day came. I stood out there like everybody else and froze to death while waiting for the events to happen. And figured, "Okay. Did that. Now I better figure out what I want do next." And didn't expect, really, that there would be a call from Kathleen Sebelius to say, "I want you to come and talk to me about this job." But hearing from her and then hearing from the President that this was what they were hoping I would do. It was pretty hard to say no. And it was an exciting way to broaden my own opportunity for a landscape surveillance and maybe bring some of the skills of -- from the genome experience, but also have a chance to learn a lot of new ones.

Bob Cook-Deegan
So in a way, it's bringing the old team back together because the two of you [Varmus and Collins] used to hang out in the old nurse's quarters, right? And when you were both starting your new jobs, now you're on the transition team, and in a way, you're now the NIH director and he's an institute director.

Francis Collins:
Yeah, we did a randomized crossover trial.

[laughter]

Bob Cook-Deegan
And Eric, for you, how does this -- you become -- stepping into the shoes, in a way, of Francis Collins.

Eric Green:
Yeah. Big shoes.

Bob Cook-Deegan
Talk a little bit about the succession of Watson, Collins, Green.

Eric Green:
Yeah, I don't know how Green got in there.

It's a little intimidating. It was big shoes to fill, but, you know, one of the things I would immediately point out is, especially at the stage of becoming the director of the institute, I think my assuming the reigns of the institute, it was a very different circumstance than what Jim and Francis had. And the reason for that is that, when you explore this with each of them, when they were brought in, in each case, it was to run a project. It was to run the Human Genome Project.

That was the major focus when they arrived on the scene. And when I was asked to become the director, I was asked to come in and run an organization. And I was asked to nurture the growth of a rapidly maturing field.

That's a very different circumstance than what Jim certainly had, but even what Francis had. I think about what I had to do, you know, both organizationally and programmatically. I mean, organizationally, it really was time to look at NHGRI in the current context of what was going on in genomics and how we were nurturing and funding programs and realizing that the structure of the organization had not changed since the Human Genome Project. And clearly the field was different. We were different as an organization.

I would also say there were issues of transition at the leadership level and I had to assemble a leadership team because people were moving on or telling me they were getting their retirement, and so forth. And so I had to make a lot changes to the institute organizationally and leadership-wise. And, to be honest with you, that at times proved challenging. I mean I think I just put my head down and said that I'm going to do this. But there was some consternation, to be honest with you, by some of the people surrounding Francis in the leadership position being a little worried that, "Why is this new guy going and tinkering with this institute the NIH director used to lead? I mean, did he not know how to run an institute?"

So now it was, "Why was it such a fixer-upper?" You know, and I got a little bit of push-back every once in a while about some things. But it was never from Francis. And the fact, I think I called him about almost everything I planned to do in renovating the place. [Looking at Francis Collins.] And you agreed with it. And in some cases you even said, "You know, it probably was overdue."

Francis Collins:
It's overdue

Eric Green:
"I wasn't going to do that at the tail-end of my directorship but it all made sense."

But, you know, so organizationally there was a lot of work. And I just think that in Jim's case and in Francis' case, the laser focus was "We just have to get this Human Genome Project to be successful." So, I'm not saying mine was harder or theirs was harder. It was just very different.

I also think programmatically it was -- there was a different set of challenges that I had to face. One we've talked about a little already was really better defining "what was NHGRI's place on the NIH landscape?" Because everybody was doing genomics; what were we doing uniquely? That was never an issue earlier for Francis or Jim. I think the other thing that I faced, I certainly felt this quite strongly—[as it] was my main push early on, as visualized in that 2011 strategic plan—was to start to move the institute's research focus, extending it beyond basic genomics and start to think about clinical applications.

And I walked into tension. It's the classic tension between basic research and clinical research. And that's something that other institutes have been dealing with for decades. But I was facing it

not only with my internal staff. I was facing it with my community. Some people being very against that, or you know some people feeling I was going too fast. Others thought I was going too slow. Most people were pretty unhappy. What I finally concluded was that these issues I was dealing with, both organizationally and programmatically, these were middle-age problems. That's what institutes have to go through when they're middle-aged. Jim and Francis got to preside over an institute in youth and adolescence. And they didn't have to deal with the middle-age institute which I've had to deal with and I continue to deal with. It's just a different life phase of the organization.

Bob Cook-Deegan:
So, could each of you talk about -- one of the signature features of NHGRI has been a strong association with open science with a particular style of doing science that is: "we share, we get stuff out as quickly as we can, and we get as broadly available as possible." Talk a little bit about how that works and what you see as the signal events. Obviously the Bermuda Principles is one of the landmarks there but many, many other steps. So talk about how you think about that strategically as the directors of this place.

Francis Collins:
Well, I'm glad you brought it up because I think in the view of long-term, historical contribution, I think the open science attitude, which was born particularly out of those conversations in the genome community, is one of the most significant contributions this whole effort has made and has now spread into many different areas of biomedical research. And certainly now as NIH director, I see the evidence for that all around me, of people saying, "You have to have your data sets available."

We're making that now a requirement, not just for things like sequencing the human genome but for all manner of science that people are doing and it's become the norm. It's sort of the ethical standard that you don't hoard your data. You make sure that it's as accurate as it can be, but you put it out there. And it's revolutionary in terms of how it empowers all the bright brains that are out there to build upon what's being developed. It's crowd-sourcing in the most appropriate, positive way.

And all of that, sort of going back to that day at Bermuda which I think we talked about before, which arose -- and it might not have, because the people who were there making those decisions had no real authority to do so, but they did anyway. On the basis really, I think, of a moral argument that "you're taking dollars that people have contributed to this effort to a public program and there's no justification for not putting the information out there so that it can be used for ultimate human benefit." But we had Fort Lauderdale after that. Sort of the next go-round of, "Okay, that now is the norm for DNA sequence but what about other kinds of large-scale data." And the idea of a community resource project and the fact that if you were doing one of those, you better make your data available. The same principle applies. That was a tumultuous meeting that almost fell apart. But actually kind of got grabbed out of --

Bob Cook-Deegan:

Well, on that point, does it feel like we would have ended up at the same place anyway? Does it feel inevitable? Or does it feel like something that was highly contingent and --

Francis Collins:
I -- you know, obviously, a parallel universe where there was no Bermuda would be interesting to see. I think, ultimately, the case is so compelling for public good, and I do think public good drives decisions. Eventually, looking at our Congress right now, eventually seems like it could be almost infinite. But for this kind of argument, to not have reached this point eventually, it's a little hard for me to imagine. But it might have taken a decade or more to get there and a whole lot of hoarding might have happened. And progress might have been impaired. And science would have, I think, suffered. And the public would have suffered. And so yeah, I think it mattered a lot. I think it was a huge part of why we all look at what the Human Genome Project did and say, "That really changed everything."

Bob Cook-Deegan:
And how were the other institutes thinking about this, the same time that you all were doing your reference sequence? Were they drifting in the same direction? What's your sense about that?

Eric Green:
Occasionally. You know, some emulated. Some, I think, sort of said, "Yeah, it's not practical." Or, "I've got too many other things to deal with." I don't think there was a universal commitment. Here's one of the points I would make, because I might agree with Francis that eventually we might have ended up there, but I have to tell you, you know, I took over as director a little more than five years ago.

One of the things I inherited was a process to generalize data-sharing across the NIH for all genomic data. Because they had gone from Bermuda principles to Fort Lauderdale principles to principles for sharing genome-wide association study data. It was called the GWAS policy. And it had just started a committee process trans-NIH to get a conversion from GWAS data to all genomic data to be shared, by policy, across NIH. Intramural, extramural, and make it universal, which I think is just so obvious.

The resistance, the inertia to -- I think that if we didn't continue to put huge energy into this, you know, Laura Rodriguez and I and subcommittees and subcommittees and subcommittees of just, you know, carrying very heavy stones up a mountain. Weeks and weeks of meetings and meetings. Here we are in 2015 and we're just -- five years later. We are just rolling out this NIH-wide genomic data policy. I know for a fact. I can tell you that if we hadn't been carrying the stones up the mountain, it was not going to happen in 2015. I'm not sure it would have happened by 2020. So I think, you know, NHGRI and other converts that we have—and I think we have far more across the NIH now than we had five years ago—absolutely have to put the… it's not a matter of *if* we're going to do it. It's just *how*, working out the mechanics, how do you get this written into grant language? What are the legalities? All those operational things.

And it does take time. And there is resistance. And there's many micro-examples where we've seen genomics communities merging with disease research-oriented communities. We just say, "Well, of course we're going to share the data." And there's push-back. So, I don't believe it

would happen nearly as soon if it wasn't for the push that started in Bermuda, but that movement continues. And we're not letting up.

Francis Collins:
And people could see it really made a difference. It did result in more rapid progress. And that created, sort of, a delightful contagion where other kinds of data that had not been made public. Now people began to ask, "Well, why not?"

Look at clinical trials data. I mean, here we are, having just put out this notice that all NIH funded, in fact all U.S.-funded research in clinical trials is going to have to release the results in summary form 12 months after they collect the last data point. Shocking to imagine that, and it shocked a lot of clinical researchers to realize that this is not just a suggestion. This is a requirement. That, I don't think we would be in that space with that kind of data if we hadn't first shown with genome data how valuable it is to just get over it. This idea that you can hang on to your data for indefinite periods of time until it suits you.

Bob Cook-Deegan:
And you grew up in human genetics, where that clearly was not the norm.

Francis Collins:
Well, you could say that, yeah, the human geneticists were not exactly role models in many ways. They were some of the worst offenders in terms of unwillingness to share samples, share data, share anything.

Bob Cook-Deegan:
And, in fact, in a way, the two of you represent a generational shift within human genetics. [Looking at Eric Green] You're growing up at one of the epicenters of yeast and nematode biology that is this open science, "we share everything along the way."

Francis Collins:
I'm glad you mentioned nematode, because I do think what was done was *C. elegans* was a really important sort of setting the stage, and when we had that Bermuda meeting, it was Sulston and Waterston who were particularly powerful in convincing everybody that you have a lot to gain by immediate release, and you have no way of justifying the alternative.

Bob Cook-Deegan:
So I wanted to -- we're getting near the end of time, and I want to ask each of you… Here's your chance. If you… Is there a part of this story that just doesn't feel quite right in the previous accounts that are out there in the world? Are there things that you wish the world knew about? Or, go another direction: What are the things that you think are most memorable or most significant about your respective periods as the directors of this institute?

Francis Collins:

I guess what sticks in my mind most is the ability to pull some of the most creative, energetic, brilliant people, who would have been doing something else, together to work as a team on these projects. And yeah, I do remember sometimes where that was not easy, and difficult conversations had to be had, but mostly I remember how impressed and inspired I was by how people who could have demanded to get all the credit, because they had the skill sets in any other field that that would have been likely to happen, they were willing to say, "No, no, the goal here is what matters. We're going to do this together. We recognize that nobody succeeds unless everybody succeeds." And to have a chance to participate in that culture change for science, because that hadn't really been done in life sciences before. That I'll remember. And now you see it happen much more readily, but at the time it was pretty radical. It… it was inspiring.

Bob Cook-Deegan:
What would be the story that you would tell that would most exemplify that cultural norm shifting? Is that the reference sequence itself, or is other project that you're thinking of -- about in that kind of collegial --

Francis Collins:
Oh boy, you know it's all of them, but maybe for me, especially because the sequencing and HapMap were ones where I really was in that role of trying to keep the team together, and that was not easy. I mean in the dark days when Congress was questioning whether there was a need for a public sequencing project anymore [see House committee hearing in July 1998], and the private project was making lots of claims about what they had accomplished, but nobody could see the data, so we were sort of at a disadvantage, because our data was all out there and you could see what was done and what wasn't.

There was a particular moment when the public project leaders really were beaten down, and almost ready to say, "Maybe we should just say 'let them do it' out there," and eventually maybe the data will be public, and maybe that'll be okay. That was a very intense Friday morning, and I knew that was coming. I had stayed up all night thinking about how to make the right kind of points about why this was historically so important, and why it wasn't fair the way it was being portrayed, but why everything that people had worked for was actually on the brink of working. Because this was at the point where we were just about to really take off.

Bob Cook-Deegan:
Is this like post-hearing in the House? So May, Celera announces, July the hearing happens. Is this in the wake of that hearing, or --

Francis Collins:
A little -- it's six months after that with this sort of constant barrage of PR coming at us, and many questions informally coming at us from the Congress about, why are you still there? That was a challenging time. But people got it, and needed to vent a little bit, and -- because, my gosh, these people worked so hard. I mean, what we went through trying to ramp up to a thousand base pairs a second, seven days a week, 24 hours a day, from where we had started. And constantly having to revise and make a new plan, because the technology came along to make it so. I mean, what we put those sequencing centers through month after month just when they thought there was a trajectory, and then it got shifted again, and they had to retool. Amazing dedication.

Eric Green:
Lots of whiplash. I remember -- I mean, I watched this, because I had a fairly close view, and it was a lot of whiplash, but they seemed to tolerate it because of the laser focus on what the goal was.

Francis Collins:
And it was a goal not just to say we did it, but we gave it away.

Eric Green:
You know, one of the untold things -- it's not a specific example, but it's a pattern, and I find especially as I talk to young students and trainees, especially those who were like not even born when the genome project started, and -- but --

Bob Cook-Deegan:
There are a lot of those now, aren't there?

Eric Green:
There are.

[laughter]

We read about the genome project and projects like it, and just think that there was this playbook on day one of exactly what we were going to do.

Francis Collins:
Yeah, right.

Eric Green:
I think one of the untold, or maybe misunderstood, perceptions of these large genomic initiatives, whether it's the genome project, whether it's HapMap, whether it's ENCODE, 1000 Genomes, et cetera, et cetera, et cetera. Whether it's precision medicine. Whether… It's just this -- all the -- and a lot of commonfund projects [NIH projects that apply for funding from the NIH director's office] along the way; the Human Microbiome Project, and so forth. It's the idea that when they get announced, and even when they first get funded, that there is this clear path of what we're going to do. You know, and I can joke about thinking back in the Genome Project, day one, you know, there I am, a post-doctoral fellow in Maynard Olson's lab, and you know, we were terrified. We had no idea how we were going to do any of these things.

[laughter]

And we had audacious goals, both at the project level, what you're funded for, but also the big project level. But it's true for every one of these things, that when you start you really have no idea. The fact that we put our names on a paper, you know, in 2003 that said we're going to get to a $1000 genome, and if you would have asked any of the authors of that paper, the three G's, or

FC, you would have asked, you know, "How are you going to do that?" We would have said, "We have no idea."

[laughter]

You know, we had no idea. And yet I think students will read -- will look back on that and say, "Oh yeah, 2003, they laid out a plan for getting to a $1000 genome, and they followed the plan, and there they got to the end."

[talking simultaneously]

If only they knew. I mean, but it's this -- it's a consistent pattern with every one of these things. You just simply lay out audacious goals, you say a few things about how you're going to get started to reach them, and then you figure it out.

Francis Collins:
And I've got to say, the irony of having this conversation on this day -- this is January 29, 2015 -- tomorrow morning there will be another audacious program laid out by none other than the President in the East Room of the White House, same place as where that announcement of the draft genome happened 15 years ago.* And again it'll be an audacious program where the details are very unclear, and maybe people assume that we know what we're talking about. Well in general terms we do, but most of what really has to be worked out is going to have to be worked out as we go along. That's why it's fun, actually.

Eric Green:
Right, you have to have nerves of steel, though. You're going to announce audacious things and say you're going to achieve them, and having no real idea at a detailed level how you're going to do it. But I think this institute and increasingly NIH has this track record and… This works. And I think part of it is—and I think it's the spirit that Francis was speaking to, about the participants in the Human Genome Project—is that when you can point to a goal and you get people believing in it, they're willing to come together and be flexible and nimble, because you have to be, and they'll rally around and work together to achieve the goal.

Francis Collins:
It's the genome way.

Bob Cook-Deegan:
So the high points, low points, you told us a moment, Francis, and I appreciate your sharing that low point moment. What compensatory, euphoric moments that you guys can think of that are

* President Barack Obama, having devoted a paragraph of his January 20, 2015 State of the Union Address to announcing a "Precision Medicine Initiative," on January 30 convened a formal event to announce its launch.

associated with running this place? A particular moment that just kind of captures "this is why this is a fantastic thing to do."

Francis Collins:
I guess I will revert back to my roots as a physician, and when something comes out of all of this that actually sheds a bright new light on a medical problem that was completely obscure before, those get me pretty excited. So when there is a kid whose strange disease was about to take their life and DNA sequencing turns out to explain it, and not only explain it, but explain it in a way that immediately suggests an effective action, and that kid is now happy in third grade, that's like, wow.

Bob Cook-Deegan:
So can you tell us a story? I don't know if this [is appropriate] -- probably you're not [allowed to talk about it] but I'm sure there's a back story for who was sitting in the box with the First Lady [at the State of the Union] and the…

Francis Collins:
So that was Bill Elder, who was a medical student with cystic fibrosis, and yeah, that's another one of those moments. Well you know, how long has it been since the CF gene was identified? 1989?

Bob Cook-Deegan:
I don't know. Does anybody know that in this room?

[laughter]

Francis Collins:
[Many people] in my lab banged away on that, and it was so incredibly painful without a genome to guide you. It would be so easy [now], you know? But now to have us go all the way through those many painful steps of trying to use that information and ultimately come up with an effective therapeutic and have it work so incredibly well for those people who have G551D in the mutation in CFTR, that's what Bill Elder has. And here's this incredibly healthy looking medical student [referring to development of ivacaftor and lumakaftor, drugs demonstrated effective for treating cystic fibrosis caused by certain mutations]

Bob Cook-Deegan:
Yeah.

Francis Collins:
-- who went from a pretty tough space that he was in now to, in his view, having a pretty normal projection of his ability to live a life. That's pretty amazing.

And HapMap, you know, we started out this process of trying to discover variation in the genome, and is it going to actually turn out that you can use this, and where we were early on in the process, coming up with the first -- what was it? First 95 SNPs that people tried coming up with a very

effective linkage for macular degeneration. I mean, it's like, hey, this is going to actually shed light. Who knew that that gene, C4H, was going to turn out to be relevant to this disease?

Those moments of revelation where you realize, yeah, we did all this work, we built all this really cool foundational information, and that was amazing in itself, but it's starting to go somewhere. It's starting to actually help people with really difficult medical problems. That's the dream.

Eric Green:
I would -- I mean, the euphoric moments that I've had already in five years, I would certainly say any of these examples where you see clinical home runs are euphoric for me, especially as the person who I think has really worked hard to start to shift the institute's focus to include clinical applications of genomics. And so seeing that relevance, it validates it. I have to tell you, I have a lot of micro-euphoric moments when I hear from members of the community, when they say nice things to me, and thank me. Because I have to admit, following in the footsteps of Watson and Collins, those are big shoes to fill, and at times, you sit there and say, "Wow, am I ever going to be as good as?" You know, and it's that this institute has a lot of rich history, and leading it is a little intimidating. So when I hear from people in the outside world who come up and say nice things about what's happening at the institute and my leadership of it, I have to admit I find that extremely gratifying.

I'll tell you the third thing that -- because it in many ways it also represents an expansion of genomics beyond a scientific discipline, and that is its relevance in society.

Bob Cook-Deegan:
Yeah.

Eric Green:
And I would say that one of the things I'm already incredibly proud of is the fact that we developed this partnership with the Smithsonian Institution to create an exhibition on genomics, which was at the Museum of Natural History for 14 months, and is now touring North America for five years. And I'm proud of the exhibition. But symbolically I'm proud of the fact that it's being so incredibly embraced as an important thing to do, because the relevance of genomics to society, and that genomic literacy is now so important. And to me, not only do I feel that's a great thing for the institute, but as somebody who got involved in genomics on day one of the field, as a young trainee, seeing that maturation from, you know, this geeky scientific enterprise to sequence the genome to now making it relevant for medicine to now making it relevant for society. I have to admit, that is going to be high on my list of proudest moments.

Francis Collins:
Yeah, Eric, I got to agree with you on that, and along with that, I guess another high point really was getting GINA, the Genetic Information Nondiscrimination Act passed. That took 12 years of incredible effort on the part of lots of people with what appeared to be success, always resulting in failure, and then ultimately pushing it over the finish line. And to be in the Oval Office when that was signed and then you knew it was really there, that was a high point for sure. And we had a great party afterwards.

[laughter]

Eric Green:
And then all of these things that Francis and I just gave as highlights must be the reason why genomics gets talked about a lot in the Oval Office these days, apparently.

[laughter]

And that's got to say something, too. The fact that, you know, in just a little over a quarter century -- it's a very young discipline of genomics. NHGRI has been the leader of it, and here it is, a major focus for the President of the United States in a real, substantive, and intellectual way. That says a lot about the field; it says a lot about the institute.

Bob Cook-Deegan:
Well, thank you, guys.