Questions and Answers with John Rowe, Francis Collins and Claire Fraser

DR. McCABE: We're going to alter the schedule a little bit. Francis, if you could join us down here -- well, I guess you can take questions up there as well. If you can join us at the table, Dr. Fraser, because Dr. Rowe has to leave at 3:00. So we'll do some Q&A now until 3:00 and then take our break. Dr. Budowle has agreed to take the break out of sequence.

Questions for any of these three speakers?

DR. WILLARD: Francis, can you say a little about --

DR. McCABE: Can you get closer to the mike, please? Thank you.

DR. WILLARD: Can you say a little more about the thinking about this half-million patient cohort from the perspective of the depth and the type of clinical information that one would want to have? Obviously, one doesn't want to get partway down this process and then find out that, oops, we should have been collecting other kinds. And yet, we have this wonderful, wonderful in quotes, track record of people keeping dietary questionnaires, and it's just not a terribly robust or reliable set of data, and yet that's what I thought I heard you arguing for.

DR. COLLINS: Well, this is still a sort of very early stage of any discussions on such a project, and I can't say at the present time there's even a groundswell of enthusiasm for doing such a project. I happen to be pretty positive about it because I think without it we're going to be kicking ourselves in six or seven years wondering why it was we didn't think about setting up a study that would give us an unbiased view of genotype/phenotype correlations.

But there's a whole long list of critical questions that would have to be answered. What is the right number of subjects to enroll in order to get sufficient power to make those assessments for common illnesses? You can go through the mathematics. If you draw much below half a million, you're not going to have enough incident cases, even of reasonably common disorders, to be able to draw strong conclusions about the relationship of a particular allele to the onset of disease, and particularly so if you want to intersect that with environmental data.

You're asking a very good question: What kind of environmental data should one collect, and how sophisticated can we afford to make that in terms of the cost of the enterprise? Dietary questionnaires would be a small part of this. Obviously, you want to know about more than that. You want to know about exercise, you want to know about smoking, you want to know about alcohol, you want to know about work, you want to know about stress, and there are certainly people who have studied those kinds of issues to a considerable extent, but it's certainly never been contemplated to apply something on quite this scale.

We certainly talked with our colleagues at the CDC about this. Obviously, the NHANES experience is one to look at in terms of an enterprise that's tried to do some of those same things. But I think before one would even think about starting a project of this sort, you would have a couple or three years of a very careful planning process to try to pick the brains of everybody who has useful ideas to contribute about how to design such a study, as is currently ongoing in the U.K. with their BioBank project.

DR. McCABE: Because we don't have much time, I've got Reed, Chris, and Debra, and that will be it before the break. So please try to keep your questions and your responses brief.

DR. TUCKSON: After the wonderful, vigorous ethics discussion at the very beginning, I would have liked to have asked Jack more questions that would have elucidated the comments he made, which I thought were terrific. But I'll have to pass on that part.

DR. ROWE: I'll take advantage of this, because I wanted to follow up on something that Francis said which is very important to me and to Aetna, and I think to all of us, and that is with respect to the issue of racial and ethnic disparities. Unfortunately, there appear to be data to indicate that certain racial groups, particularly African Americans -- and I haven't seen the primary data here, but this was reported to me -- are much less likely to be willing to have genetic tests and much more concerned about issues of discrimination, which is understandable.

But if that's the case and if that plays out with respect to the clinical application of genetic tests, this is just going to further aggravate the racial and ethnic disparities we have with respect to being able to provide people with access to appropriate care, et cetera. So this is, unfortunately, in the wrong direction and is an issue that I think would be particularly important with respect to the education of physicians so that they will be aware that there may be some reluctance and particularly motivated to make sure that the patients who fit into those important populations did have the opportunity to have tests that would be appropriate for diseases that they were at risk for.

DR. TUCKSON: What I'll do is just ask Francis, and maybe we can come back to it for a deeper discussion.

I want to have a little bit of assurance on your research agenda. It is a very big agenda. You talk about diabetes, cardiovascular disease, cancer, psychiatric disease, arthritis, asthma, and right now we've got basic research in all those areas. We've got therapeutic interventions being developed in each of those areas, and diagnostics. We've got a health services research agenda to worry about. We've got a CDC preventive agenda to worry about in all those, and it sounds sort of like there is, although listening carefully I don't think this is what you called it, another set of research agenda.

We've got to feel confident at some point that somebody in this government is coordinating all of these things so that things are not additive but they're synergistic, prioritized, and some sense of sequentiality, that one thing is related to another and to another. Unfortunately, as a member of this Committee and really a member of the public, we don't hear that articulated. So it sounds like these are mutually competitive agendas, and I hope at some point we will have time as a Committee to delve into that.

DR. COLLINS: I would like to reassure you that that is not what this document aims to try to put forward. Clearly, the ambitious nature of the milestones that are described there would never come to pass without the participation of lots of other entities, just well beyond the Genomics Institute at NIH. If you look in some of the language that's in that document, it repeatedly talks about this is only going to happen with partnerships, partnerships with other NIH institutes that have specific interests in particular diseases, like diabetes or heart disease.

We see genomics as providing some tools, and that's certainly what my institute hopes we can do. But the application of those to specific diseases goes well beyond anything that we could contemplate or should contemplate doing by ourselves. Similarly, as in the example of this large-scale cohort study, the kind of collaboration between NIH and CDC that would be necessary to make this happen, and in fact other

agencies within the department as well that have already been represented in this group, like HRSA, for instance.

So I would like to be somewhat reassuring that although it may seem as if all of these various plans are occurring in silos, my own experience after 10 years of being here is that that really is often not the case. In fact, it's usually not the case. One does identify ways in which agencies have shared missions, and we work on them together and not in isolation from each other.

DR. McCABE: Thank you.

DR. HOOK: This is a question for Dr. Collins, but it follows up on what Dr. Rowe has just mentioned, and that is the issues of racial disparities and racial attitude toward genetic testing. In the 500,000 epidemiologic project you're discussing, how much of that is planned to include adequate numbers of minority individuals? How do we ensure that they will participate? Are we going to have to expand it to make sure that those data are appropriate for all the different populations we represent?

DR. COLLINS: That would be absolutely critical because, as I outlined it again, please don't assume that this sort of idea that I floated in front of you this afternoon is one that's already been fleshed out in a lot of detail. It certainly has not. But for this to be a defensible project, it would have to be set up in a fashion that sampled adequate numbers of minority populations to be able to draw meaningful conclusions, and certainly that would have to include in this country African Americans and Latinos and Native Americans, and perhaps others as well, in the same way that the NHANES effort that CDC has done, which I mentioned as a possible pilot, has done that same sort of oversampling in terms of relative numbers in order to be able to draw conclusions that are meaningful across populations.

All of that would then have to deal with the issue already pointed out about reticence, and even suspicion on the part of some members of some populations about research in general, and particularly genetic research given the history of sickle cell disease and carrier testing for that, which is still resonating in many people's minds and which was a very unfortunate experience back in the 1970s.

DR. LEONARD: I don't mean to beat a dead horse, but this large patient cohort with genotype/phenotype correlation is, I think, essential to achieving that correlation between genetic variation and all these different diseases that we talk about. If that is not in place somehow, then I think all the benefits that you're talking about are not going to happen. So this is already happening in the private sector, and my fear is that there will be -- or my concern is that there will be privatization of this type of information as private cohorts are created, cohorts of patients.

Is there any way that policies or recommendations can assist in moving this project forward in a public manner so that it doesn't get privatized, as we've seen with other things?

DR. COLLINS: I don't in any way think that it's a bad idea that there are private-sector investments going on in cohorts of this sort. I think they are, in general, not going to be like what I'm describing, which is a large-scale, covering all disease kind of enterprise. They will be cohorts focused on specific diseases for specific drug response clinical trials.

DR. LEONARD: No, there are private ones that are just "send in your buccal swab and your medical information" that exist now.

DR. COLLINS: Okay. But to what extent are those aiming to accomplish this kind of large-scale genotype/phenotype correlation, collecting all of the kinds of additional data I mentioned? I would be

doubtful that there's something quite on that scale that would make business sense in terms of being able to accomplish what we're talking about here.

Never mind. Just the same, I think it's critical to have a public effort of this sort if you're really going to be able to have the kind of input that we would all want to see in the design of the study, if you're going to get public participation on the scale that's expected here. I mean, I would hope that participation in a study of this sort would be seen as sort of a badge of a U.S. citizen of a particular dedicated sort, that I'm part of the United States National Study of Health and I'm going to be enrolled in this study for the next 10 years and undergo questionnaires and some additional medical testing that otherwise I wouldn't because I want to do something to help understand why some people are healthy and some people are not, and maybe this will be a contribution I can make to my family, to my community, to my country.

DR. LEONARD: We need to do it.

DR. McCABE: With that as a comment, you can sign up for Francis' study. There's a sheet at the registration table.

(Laughter.)