

**DISCUSSION OF JUNE 2010 SACGHS SESSION ON THE  
IMPLICATIONS OF AFFORDABLE WHOLE-GENOME SEQUENCING**

CHAIRMAN TEUTSCH: Anyway, our first topic is to talk about our plans for addressing the issues surrounding the affordable genome. This is a topic that has come up repeatedly over the last few years and, as we near the time when the affordable genome is likely to be a reality, we thought it would be important to actually take it up as a topic in its own right.

The next generation sequencing methods are bringing the clinical use of whole genome sequencing data closer to reality. We know there are a variety of technological issues but they seem to be being surmounted but there are a lot of downstream consequences to the affordable genome as well and how that information can be and should be incorporated into clinical care.

In Tab 3 of your binders is not only some articles which hopefully you have had a chance peruse but also a set of questions. What I would like to do is spend a few minutes this morning having a discussion

about what all of you see as the issues that the committee should be taking up so that we can begin to formulate our plans for the future.

So I will open the floor to thoughts about how we might--what are the kinds of issues we should be taking up.

(Pause.)

Good, Mara, thank you.

MS. ASPINALL: Well, first I'm going to ask a question.

Have we received any specific guidance or questions from the Secretary or from the Secretary's office of high-priority issues, whether short-term or long-term, that the Secretary would like us to consider?

CHAIRMAN TEUTSCH: To my knowledge we have not received any such things but when I met with Dr. Collins-- Back when? In September? --this was clearly one of the items that was high on his priority list and thought was a way to bring together many of the things that we have been dealing with in terms of DTC and oversight of genetic testing and clinical utility

assessment, all of those sorts of things.

MS. ASPINALL: "This" meaning the implications of the affordable genome?

CHAIRMAN TEUTSCH: Yes.

I think what we are looking for here is your sense of what our priorities are. What are the issues that you see if we're going to take up the topic of affordable genome and-

MS. ASPINALL: Oh.

CHAIRMAN TEUTSCH: I'm sorry if I miss-

MS. APSINALL: No--

CHAIRMAN TEUTSCH: --so there are technological issues that we want to talk about. We may want to talk about issues surrounding how it gets incorporated into DTC or where it fits in with clinical testing, where it fits in with newborn screening, where it fits in with--what are the downstream consequences because--okay--we have a \$1,000 genome. There are enormous human consequences. There are clinical downstream testing, all kinds of things that would need to be done. So we have a broad range of topics we could be taking on. My guess is we will end up forming

a task force to help us with all of that and have some informational sessions but we would like to get your thoughts about where we might focus our energies.

Gwen?

Gwen and then Mara.

MS. DARIEN: I was just—one of the things that occurred to me is that this ties into the whole—some of the work that we did on the DTC task force, especially as it relates to the clinical utility of an affordable genome if people are doing it outside of a provider context.

CHAIRMAN TEUTSCH: Mara?

MS. ASPINALL: Jim was first.

CHAIRMAN TEUTSCH: Oh.

DR. EVANS: I was--

CHAIRMAN TEUTSCH: Mike.

DR. EVANS: Yes, I was going to echo what Gwen was saying. I don't think--in reading the materials beforehand, I don't think that we should focus on the proximal issues, that is what are the challenges in closing the gap between the \$10,000 and the \$1,000 genome. That's happening and I

think that's going to happen with or without us much more rapidly than we can mobilize. I think that we should focus on downstream issues and keeping in mind the kinds of things we've always emphasized, I think clinical utility is a big one. And I think the other Gwen also alluded to. I suspect much, if not most, of this type of sequencing will be done outside of the clinical arena and will only filter in to the clinical filter in roundabout ways because people bring their genomes to providers, et cetera. So I think we should focus on interpretation and trying to bear it out clinically.

CHAIRMAN TEUTSCH: Okay, Mara, and then Muin.

MS. ASPINALL: So I would agree as well that we should assume that there is an affordable genome and define affordable at the beginning of the report because some would say an affordable genome at \$1,000 isn't truly affordable but that we get to that piece. I would probably be less inclined to focus on the clinical utility issues but rather take an assumption that if there are tests within there that have important clinical utility and say, if indeed, that is

the case, similar to what we did in the early years with genetic testing, here is talk about, in my mind, three areas.

First being the health IT piece, which clearly how is--what are the implications in terms of data that comes out of this, both from a magnitude of data and the issue around privacy of data and how that data, especially if it's done outside of the traditional system, is shared or not shared.

Secondly, I think the issue of the payers and starting with the public payers is an issue. So if, indeed, someone who is on a public payer system has information, how is that integrated or not into their care, what are the implications for reimbursement for the testing or the implications related to that.

And, lastly, with maybe Education Task Force, what this means for physician education in the broader perspective as to if, indeed, this is available and everyone is bringing it to--lots of people are bringing it to their physicians, what kind of information does the physician need to be equipped with in order to best integrate or choose not to integrate that information.

So to me those are the three core areas.

CHAIRMAN TEUTSCH: Let me push you on one thing. You said you would not focus on clinical utility. Given that there's obviously a huge amount of information, some of which is actionable, presumably related to health benefits, but also a huge amount of information we don't know what to do with or would lead to additional testing that may be good or ill that you don't think that's an issue that we should be taking up in this context? Not necessarily gene by gene but as an overall how to think about the problem.

MS. ASPINALL: I would very much agree with your conclusions, lots of actionable items now, lots that isn't and that may flip-flop and change over time as we learn more. My concern is the amount of time and effort it takes to put together an assessment of the clinical Utility maybe beyond what we can do in this committee in a reasonable amount of time. So it's not to say that it's not important to be looked at. I see that less as our core competencies to do in the period of time that I think this is relevant. So I think it's—as I've said, there have been a couple of areas

before more important to have a core of opinion on some of the issues than a lot of opinion on something else if it takes another year to get there. So my issue is that clinical utility is a bigger nut than we can crack short-term.

CHAIRMAN TEUTSCH: Okay.

Muin?

DR. KHOURY: Okay. Well, I think this dialogue between you and Mara sort of jogs my memory here that probably clinical utility is the most important thing that this committee could focus on and the fact that it will take some real-time effort and studies and money to establish the clinical utility of the personal genome should not discourage us from doing it. After all, we spent billions of dollars to get to where we are now and, I think, it's very important to evaluate from a societal perspective the balance of benefit and harm.

I agree with you, Mara, but there are actionable things in the genome but many more non-actionable things but people will take action on the basis of these. They might even remove their prostate

or, you know, other more drastic surgeries as a result of knowledge of the genome.

So I think in addition to all what you said, I think the importance of the balance of benefits and harms has to be explored from a societal perspective.

I just wanted to refresh the committee's memory here. Last year CDC and NIH held a workshop on personal genomics, the results of which are published in Jim Evan's *Genetics in Medicine* illustrious journal here, for which many people, including Francis Collins—I think, Steve you were on that committee—made some recommendations for actions. So I think it's important to put that in the context of what we are trying to do here.

If you think that we are struggling with what to do with one million data points, we ain't seen nothing yet. I mean there will be three to six billion data points and how we deal with that from an IT perspective, from the act of consumer education, or whatever, I mean it touches on all the areas that this committee has been exploring over the last few years, including clinical utility.

CHAIRMAN TEUTSCH: Sylvia, Marc and Mike.

DR. AU: I think it's really important that I urge the committee to keep the report as practical as possible because with the whole genome sequencing there's so much public health issues.

And if we were doing this in newborn screening, the whole shift in paradigm in how medicine is going to be given to families because if you have your whole genome from the time you are a newborn, you know, what does that mean because we usually don't test minors. There are a lot of legal issues. There are patent issues. I just want to make--there's education issues. We don't have the workforce. We don't have an educated public.

So the practical issues, I think, are what need to be highlighted to the Secretary that these bring all those genetic discrimination concerns that we have, all those reimbursement issues that we had concerns on, the education or patents. So this really--again, like direct to consumer--brings back some of the prior reports the Committee has done and really to show that this is going to make all of that explode even

faster.

DR. WILLIAMS: So I would make two points, probably both of them relatively less practical but I think philosophically very important. One is that the issue of whole genome sequencing is really not going to be--we can't look at it from a paradigm of what we have traditionally been doing relating to testing. This is really going to be a huge problem of knowledge management. It's not going to be an issue of understanding all of the different data points. It's really--we're going to have phenomenal amounts of knowledge and we're going to have to manage it in a different way if we're really going to understand how to do it. So I would--for the session I think that we would be well-served to hear from someone who has a content expertise around knowledge management.

And then I think the second area that is important to consider as we're--I am kind of just--just it slipped away here for a second so hang on. Let me just get it back. Oh! I think that having some of the people--the person that comes to mind specifically is Zach Kohane--who have written on the incidentalome. The

idea that, you know, we have faced some of the problems that Muin an Mara have mentioned before, which is we are going to find some things that we know what to do with but we're going to find a lot of things that we don't know what to do with and they do have implications. And certainly at least when that was looked at from the perspective of say whole body scanning there were some very interesting concepts that from looking at that process that I think could potentially be relevant here as well. So I think someone that has done some thinking about what do we do with incidental findings, what's the response that people have to information that they don't know for sure what to do with, those are conceptual things that I think are going to be necessary to frame this.

CHAIRMAN TEUTSCH: Mike, and then Jim, and then Charis.

DR. AMOS: Jim, did you want to say something relevant to follow on to—

DR. EVANS: No, you go ahead.

DR. AMOS: All right. I just want to bring to mind some of the practical issues that probably the

Committee might want to consider, things like data quality. It's not--data--you know, base colony is not perfect yet and so the issue of that. Integration of, you know, the whole genome with electronic health record because it's going to have to be--you don't want to have these things separate because both are going to be important; interoperability of the systems that are used to store the data and to manipulate the data. If all sorts of different companies make these systems independently then they will never be able to talk to each other and they won't be able to be useful.

Data security is absolutely critical and data transmission. The issue of just moving large amounts of genomic data from one place to another with perfect integrity is not simple, not trivial.

And then I think probably the most important thing is developing the systems to connect the genome to the--the genotype to the phenotype because genotypic information in and of itself is only as important as it relates to the patient. And there are some really, you know, practical issues of how to do that. We've actually been talking to the National Library of

Medicine on how to integrate the systems to standardize the way that genotype is annotated and integrate that with electronic health records. So it's not only beneficial to the current clinical situation but also downstream for any type of large scale clinical studies.

CHAIRMAN TEUTSCH: Great. Jim?

DR. EVANS: Yes. I just wanted to try to focus for a second on what our main role and our capabilities are as a committee. I think, like Mara points out, this is going to be an absolutely huge issue, right. There are going to be gigantic issues having to do with utility, with privacy, with the medical record. And, therefore, since it is such a big task, I think probably the best thing we can do is help the Secretary prioritize what the most important aspects are.

And, you know, I would again come back to the point that even though--well, like Marc says--this is a qualitative game changer with all of this information but, having said that, the rules haven't changed about the application of this kind of information to clinical

medicine. We have to, I think, continually enforce to the Secretary that all of this wondrous information and all of these great ideas still need to prove out as actually useful to patients. And I think that that--we need to focus on perhaps a role of prioritizing and triaging for the Secretary because we sure aren't going to be able to solve these problems ourselves.

CHAIRMAN TEUTSCH: I understand Sheila has joined us.

Welcome, Sheila.

Charmaine?

DR. ROYAL: So Mike already--

CHAIRMAN TEUTSCH: Turn on your mike.

DR. ROYAL: Mike already made one of the main points that I wanted to make in terms of integration of the information with other information about the patient or about the person who is tested, and then to piggyback on Sylvia's point about public education, I think that how people use the information, what happens when children get tested, how they handle that. So I think the public education piece of it is major.

CHAIRMAN TEUTSCH: Andrea, and then Eric?

DR. FERREIRA-GONZALEZ: I agree with every comment that has been made but I want to point out two different issues.

CHAIRMAN TEUTSCH: Could you talk into the mike?

DR. FERREIRA-GONZALEZ: I think we have two different--or more than two different issues but I want to point out issues that need to be brought out to our attention.

One of the things is that the \$1,000 or affordable genomes happen--it's going to happen. It's just--there's a race to continuously decrease the cost that it's going to happen. Issues about data management are also being dealt with expeditiously but they still will need some help.

But I think from our Committee point of view we can look at some of these more--issues that are practical to what we are going to foresee they are going to be needing to bring these type of testing or type of information into a clinical electronic medical record.

We know there are informatics needs for

standardization of vocabulary. Today even for other genomic information we don't have a genetic standardized vocabulary. So these are crucial issues that are important.

The issues around analytics, around quality control, mentioned by Mara, it's crucial how we are going to call these issues but also how we are going to do proficiency testing for these. So these are things that we can start prioritizing or identifying for the Secretary maybe somebody else can work but we can do these.

There are interface issues between connecting devices, not only connecting devices but interoperability into the different systems. So these are practical issues that need to be solved or we can bring to attention.

The other component to this is how are we going to practice having the whole genome sequence there. Who manages the information? How are we going to coordinate information, do education and so forth? So maybe we can start looking at these issues from the practical point of view that will affect how we

practice and then also I think the clinical utility is a huge issue that we need to deal with, so just looking at different aspects, not just the clinical utility.

CHAIRMAN TEUTSCH: Eric, and then Paul.

DR. GREEN: The only point I was going to make, and I've heard several speakers allude to it, I think Jim Evans said it directly and I just want to emphasize it, is I would hope the discussion doesn't try to focus on subtleties related to whether it's a \$10,000 genome or a \$5,000 or a \$1,000. What I can tell you just in two months of being NHGRI Director but prior to that for the previous 12 years being the head of a production DNA sequencing facility and so having some expertise in this area that the pace at which these technologies are advancing is truly breathtaking. I know it sounds very—you know, just like there's a wow but truly—I mean, I have been involved in production of genomics for almost 20 years and what I see happening now in sequence technologies, even in the past 12 months, is truly spectacular.

So no matter what you think you are planning, what issues you are dealing with, trying to get to it

is almost impossible. It's happening faster than a committee like this can even operate. So I would really think very ambitiously as to the amount of data that is potentially going to be generated. And all the discussion about bottlenecks of information handling, connecting it to phenotypes, to patients, to medical types, all of that is real and then probably multiply it times five.

And what I--there's no sign that the pace at which these technology advances--there's no sign it's slowing down. What I've probably learned in the last six weeks, announcement after announcement after announcement, phone call after phone call I've gotten from some of these--both the vendors but also scientists who are working on this, it is absolutely here and it's going to--the pace of acceleration is going to continue.

CHAIRMAN TEUTSCH: Paul, and then Mara.

DR. BILLINGS: So I think following on that, just on that last comment, which was I think a breathtaking review of the technology at some level, I would return to the first comment, which is

affordability. You know, that said in the context of thousands of our fellow citizens not being able—you know, going to free clinics because they can't get any kind of healthcare and can't afford any of it.

So I think we do have to deal with the notion in a critical sense of what affordability of this information is and do we actually envision that all members of our society are going to present to whatever healthcare they are getting or not getting with their genome sequence in hand because I am not so sure that the pace of the technology and the pace of our being able to provide that are equal.

So then the other aspects that I would like to sort of reecho are the medical and non-medical implications of broad based full genomic knowledge. Are there significant non-medical implications of this? I don't know if there are or not. Certainly maybe to genealogy and a few other things but I don't know. I think that needs to be certainly considered.

I really do agree with the knowledge management and the whole comments about the incidentalome. Although I would ask Jim and others,

there's also a patent issue in here and-

DR. : (Not at microphone.)

(Laughter.)

DR. BILLINGS: And so there's another life for Jim. We'd like you to stay on for a few more years to deal with that if you don't mind.

So the question is do we deal--you know, how do we get--how do we deal or do we deal with the patent issue there?

CHAIRMAN TEUTSCH: Mara?

MS. ASPINALL: Well, that's just too easy to tee up but I am not even taking on the patent issue and maybe just a broad comment and a recommendation to the committee is Wayne Gretzky had a great quote, the hockey player, which is when somebody asked how he scores all those goals and he said, "Skate to where the puck will be; not to where the puck is."

And that to me has to be the overriding principle with the comments both about the technology and the movement going forward. We need to skate to where the puck is going to be and that alone will give the Secretary insight that given the thoughtfulness of

this Committee I think we can do in a very unique way.

CHAIRMAN TEUTSCH: Jim, and then why don't we figure out what our next steps are.

DR. EVANS: So in a spirit of camaraderie, I am not going to—with Mara, I'm not going to talk about the patent issue either.

(Laughter.)

I did want to just bring up one kind of interesting thing. When you think about the whole issue of privacy, I think it behooves us to think about what drives that. And, to me, what drives that, the reason that people accord their DNA and their genetic information some increased level of protection or privilege is that it can tell us something about the behavioral aspects of a person, something about our proclivities towards certain behaviors, et cetera, and that kind of gets to what Paul was talking about, the non-medical issues. And I think that's germane to a consideration by this group because it brings up the issue of whether parts of the genome should be treated in the medical record, for example, in the same way that, for example, psychiatric information is accorded

special status in the genome.

So I think we--it might be worthwhile, it might be productive to not think about human genomic information as a monolithic entity but to think about the qualitative differences in the information that will arise and whether those should be accorded different treatments.

CHAIRMAN TEUTSCH: Muin?

DR. KHOURY: I like the Gretzky's "where the puck is" analogy and just following the puck, at least the way I follow it is it's not about technology, it's about health. And I think that's--to the extent this information, like any other biomarker information, can improve health and can be affordable and can be used by all segments of the population, I think, we will have a winner. Otherwise we will have a mess on our hands. So I am hoping SACGHS will tackle all of these things.

CHAIRMAN TEUTSCH: David, and then--

DR. DALE: An interesting discussion. I am glad we have taken this up. And I agree with Eric that the price tag shouldn't be the focus. It looks like we have established the price.

The key thing in my mind, I think, that goes along with some of Jim's comments, is somehow to be in the position of helping to integrate the scientific development of technological development with the physician's office based problem of what do you need to know and what do you need to do. We need to help as much as we can with thinking about that process as given that the genome is going to be sequenced for somebody somewhere, somebody is going to need to know then what do I do with the information. And I think that's not a very orderly process at all right now. And if we can define these steps or help to define those steps, we will really do a service to our colleagues in the country.

CHAIRMAN TEUTSCH: So I am hearing a lot of enthusiasm for lots of different issues.

I just want to say one thing, before we bring some of this together, on the affordability issue. In fact, my guess is whatever the price of this is going to be, that's the smallest part of the cost of the test.

DR. : Yes, sure.

CHAIRMAN TEUTSCH: What's going to happen is other consequences of it and it's going to be cost-inducing and presumably benefit inducing. We need to understand what all of that is going to be about.

But hearing sort of the array of the issues that are out here, this isn't about whether this technology is going to come; it's really about how do we bring it to reality in a way that enhances the health of the population.

My suggestion, and I think having heard from others prior to the meeting, is that we use some of our time at the next meeting, which I believe is in June, to have an informational session so we can all get up to speed on various aspects of this and then probably form a group to help us create a charge.

Does that seem like a reasonable plan?

So we will need folks to help us pull that together, at least for June.

And presumably on—I know, Paul, you expressed interest in that.

And Charis is raising her hand.

Could I ask—Paul, this is perfect. As

someone who has been around the block here with this, you can help.

And, Charis, you'll help because I'm afraid we're not going to get this done so fast so that will be great.

And then I think if you need more, you can draw on others but my guess is following June we will probably expand the group to figure out how we will go from that information session on to a working group.

Great! Well, thank you. That should be an exciting process and an important one.

So having seen the baton apparently passed to Marc, we will turn to the Task Force on Clinical Utility and Comparative Effectiveness Research, which we discussed last in June of 2009, and we established a task force that Marc chairs to help create a charge to identify the issues that we should explore.

So, Marc has been working diligently on that and will give us information about what he proposes we do that will be constructive in this actually pretty new and changing area, and one that is particularly challenging, I think, right now because we don't

actually know what's happening with all of the funding  
for comparative effectiveness in the health reform bill  
but take it away, Marc