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for the Study of Bioethical Issues

TRANSCRIPT

Member Discussion of Recommendations

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DR. GUTMANN: Okay. We are going to jump right into our first session.

So, yesterday we began with some of our recommendations and had a very, I thought, productive discussion of them. Today we are going to continue with them.

They clump into two big categories. One is consent to hold genome sequencing and to the possible findings and how they will be treated, and the other is oversight of them.

So, I am going to do, as I did yesterday, read draft recommendations and then ask Commission members and anyone in the audience who would like to comment on them. We are less worried about the precise wording at this point than the actual substance of what we want to recommend.

So, we left off, we did four recommendations yesterday, and we are on Recommendation 5. It in draft reads, "Researchers and clinicians should evaluate and adopt robust and workable consent processes that allow research participants, patients, and others to understand who has access to their genomic sequences and other data that are generated in the course of research, treatment, and consumer-initiated sequencing.

"Consent processes should ascertain participant preferences at the time the samples are obtained, so that participants might choose whether or not to participate or whether feasible limits on the use of their samples and/or data can be agreed upon."

DR. SULMASY: Just particularly in light of yesterday's discussion, although the first sentence is already a little long, and so the drafting might make it into two sentences, I think we need, as it stands now, to put something at the end that would say, "and how these data might be used". Because we are referring in that sentence just to

access, but I think that it is important that somebody who is consenting know how the data are going to be used. So, I think that is important to add.

DR. GUTMANN: I am going to move on to the next recommendation.

DR. HAUSER: Sorry. So, I would have one more suggestion, not for the recommendation, but perhaps for the discussion, which is that, especially in our Recommendation 1 we focus on flexibility in terms of consent and options to submit data based on consent to open access versus not open access.

And I think that we should make a point here, if the other Commissioners agree, that we should extend this flexibility very clearly to an option not to deposit data into a public database with government-funded research when the purpose of the study and the consent process does not make that feasible.

And I think the same recommendation could help guide journal editors, some of whom have policies that only open access sequenced data should be acceptable for submission to their journals.

DR. GUTMANN: Yes. I mean, I think that is one important part of what needs to be put in the text. Because this could be misconstrued, and it won't be as you see the next recommendations, but it shouldn't be construed as to say that there needs to be a long list of -- this is another point that I am making, but it is a companion -- a long list of everything that could possibly be used, because that, basically, obviates our earlier recommendation of how we are recommending that people be able to consent to, as long as they know clearly what they are consenting to, to some broad uses.

And what you are suggesting is they should also be able to say what kind

of database that they are consenting to. Okay.

DR. KUCHERLAPATI: I mean, I just want to point out, make sure of the intent of the Commission. As you know, at the present time in terms of genetic testing for research purposes, there are extensive informed consent forms that have to be read and understood and signed by the individual.

But sort of in the clinical testing, basically, if the physician deems it necessary that a particular test should be done, like any other blood test, they would order it. There is not as extensive a process of consent, even though there is a simple process of consent.

And I just want to make sure that the Commission is not recommending, or whether it is or not recommending, that the kinds of extensive consent forms that would be used research be used for clinical testing or not. I think it is not maybe clear in this recommendation.

DR. GUTMANN: Well, the next recommendation, Recommendation 6, is -- and we will move on to that after Nita's comment -- I hope really specifies what should be on a consent form. There you are comment is very pertinent because we need to say there what we intend between clinical and research.

Now just the philosophical point, which is a practical point as well here, there is a reason why consent in the clinical setting is made simpler than in the research setting. That is, there is a direct benefit to the patient in that setting. And therefore, there is less of a burden put on incidental things that are not harmful to the patient.

That said, I think your point is absolutely to the point of Recommendation

6. And so, we will get to that in a moment.

But, first Nita?

DR. FARAHANY: So, your response to Raju is helpful. I have been reading 5 and 6 together to try to understand really what the difference between 5 and 6 is. So, I will hold my comment on 6 for a moment.

Five, I am trying to understand exactly what we are asking to be done by this. So, this is one of those times where I am wondering if it is specific enough. To the extent that the answer is, well, we are more specific in 6 as to what we want for consent procedures, in 5 I am not sure what we are really asking to be accomplished by this.

And so, I would love a little bit more understanding from others as to how they see this both to be different and how they see it to be guiding.

DR. GUTMANN: So, I think the most helpful thing, because I have a similar question and I think we can only answer it if we go on to 6, is to go on to 6 and see whether these are genuinely two separate recommendations or one long and necessarily detailed recommendation. So, let's go on to 6.

Six says, and you will see how much more specific it is than 5, "The Office for Human Research Protections or another designated central organizing agency should establish clear and consistent guidelines for informed consent forms for research funded by Common Rule agencies, that involves whole genome sequencing." Now notice here, it is research, not clinical practice.

"Informed consent forms should, one, briefly describe whole genome sequencing and analysis; two, clearly state how the data will be used in the present study as

completely as possible. State how the data might be used in the future and explain the degree to which the individual will have control over future data use. Three, define benefits and potential risks as clearly as possible and, four, state what data might be returned to the individual."

DR. ARRAS: So, as we were discussing at the end of yesterday's session, we have heard over and over again that there is an impending merger between clinical practice and research in this particular area, which does raise the question about whether the standards for consent to clinical care should begin to look more like the standards of research if they are, indeed, going to merge in the way that it is anticipated.

So, I would like to hear a little more discussion about why that should not happen. Because it seems to me that if the results of these clinical examinations and tests are going to be pooled into the research community's agenda, patients should be made aware of that and made aware of the risks, and so on.

DR. GUTMANN: Christine?

DR. GRADY: I think, though, John that there is a big difference between making people aware that their samples might be used for research and in the context of clinical care where they are giving them for a diagnostic purpose or some clinical purpose and the extensive rules that govern/regulate research.

So, I think I would not want to say that all the rules that govern the conduct of human subjects research that are found in the federal regulations should govern clinical care. That seems excessive to me.

But I do agree that people who are giving their specimens for whole

genome sequencing in the clinical setting should be made aware that these will be used for research. And that is part of what Dan was saying before about the uses, the possible future uses. It seems to me both of those are doable without making them one and the same.

DR. GUTMANN: Dan?

DR. SULMASY: Yes, in light of that, that seems to me to be a reason to at least put it as 5A and 5B, if not keep it as 5 and 6. Because 5 is very broad. I mean, it covers non-federal research. It covers clinical care, as it is described, and we might flesh out a little bit of what those implications might be in terms of making sure that, even in clinical settings, it includes consent that is informed by the knowledge that these may be used for other sorts of purposes.

Whereas, 6 I think is very specific to federal research and the Office for Human Research Protections, et cetera. And so, even if we merge them into one, it should be sort of 5A and 5B to sort of keep that clear.

DR. GUTMANN: Then, the fortuitous consequence of that recommendation, the recommendation to merge, is that the first part actually does speak to clinical uses and says that they ought to ascertain a set of consent with regard to patients in clinical settings.

But, then, it goes on to be more specific in the research setting where there is no direct benefit to patients, the more specific. And I think I get the sense from this group that we want to do both, but we don't want to saddle clinical settings with as extensive set of requirements.

Anita?

DR. ALLEN: I want to speak to a different issue than the question of the merger.

DR. GUTMANN: Sure.

DR. ALLEN: So, if others have comments about the merger question, they should probably go --

DR. GUTMANN: No, I think we -- okay.

DR. ALLEN: Okay. I just wanted to raise a question about consent having to do with what we are implicitly accepting or recommending with respect to consent and minors. The way federal privacy laws generally treat minors is inconsistent. I think that we shouldn't assume that there won't be questions about whether or not minors have their own capacity to consent, right to consent, and at what age that consent kicks in.

What I have in mind is that, for example, under our education privacy laws, until age 18, parents have the right to make decisions about the accessibility of children's educational records, sensitive education records.

But under our internet children's privacy laws, the parents only have a right until age 13 to bar children from giving out information to website operators.

And then, under, of course, state mental health laws, it is often at age 14 that children have the right to make their own behavioral health decisions.

So, I am puzzling over whether there is any argument at all that youth or children should have the right, co-extensive with their parents or instead of their parents, to make certain decisions about the collection and sharing of whole genome sequencing data. And it is just a question.

I am guessing that we were probably assuming that, of course, it is healthcare; parents have a right to decide. But it is not clear to me, if we take privacy seriously, that it isn't the case that at age 13 or 14 or 18, or at some point the child's own consent or assent, or something like that, is an important part of the ethical framework.

So, I just wanted to throw that out and to see if anybody else was concerned about that set of issues.

DR. GUTMANN: Does anyone want to address that issue before we move on to others? I have Raju and Nita on my list of hands that have been raised. But on that particular issue?

Because I think it is fair to say that we are spending a lot of time, as a Commission, thinking about children with regard to medical countermeasures, which we will move to later, but we have not spent much time in this particular case.

DR. ALLEN: Concretely, I think, at a minimum, we should in our discussion of the consent issue flag this question.

DR. GUTMANN: Right. Right.

DR. ALLEN: Yes.

DR. GUTMANN: No, I think you see a lot of nods on that.

Christine, did you want to address this particular --

DR. GRADY: I just want to say I think that this is a place where, perhaps correctly, the rules about children in clinical care and research are very different. You know, what parents are allowed to agree to in the clinical setting has less restrictions. In the research setting, parents can only agree to certain kinds of research because only certain

kinds of research can be done with children.

DR. GUTMANN: Which we will get to --

DR. GRADY: Yes.

DR. GUTMANN: -- a very complete discussion of when we do medical countermeasures.

DR. GRADY: Can I say one thing about that --

DR. GUTMANN: Please.

DR. GRADY: -- in light of Recommendation 5 and 6?

I would favor not merging them because I think 5 might be vague, but it has a sort of philosophical basis of people should be given the information, whether they are in a clinical setting, a research setting, a commercial setting, they should be given the information to make a decision about whether or not they want to do this. That is what 5 says to me.

Six says something very specific about what should be written in the forms for federal research. And I would hate to see 5 diluted or misunderstood as being only around what the words in the form ought to be. So, I would favor keeping them separate.

DR. WAGNER: Christine, you said something incidentally. Did you mean that? Did you want to modify this to say researchers, clinicians, and commercial repositories?

DR. GRADY: For 5?

DR. WAGNER: For 5.

DR. GRADY: I think it has it in there somewhere. It is not in the first

sentence. Yes.

DR. MICHAEL: It is a little confusing.

DR. WAGNER: Oh, consumer-initiated sequencing. Okay.

DR. MICHAEL: Yes, I think it is implied.

DR. WAGNER: Yes, yes.

DR. GUTMANN: Yes. Raju?

DR. KUCHERLAPATI: I want to address John's question, if I may go back. I think, Amy, you addressed it in part.

One of the reasons for the excitement about all of these technologies is that we would be able to diagnose disorders that we were not able to diagnose by conventional methodologies or just clinical information alone. There are a number of examples of that nature.

And so, that means that these types of technologies would have significant amount of impact in clinical care. At the same time, we have recognized that most of the physicians around the country would have 10 or 15 minutes to be able to see each patient and make a decision about how you would be able to treat them.

Clearly, the current kinds of consent procedures that are required for research purposes are very extensive, and you need to have either the researcher or a nurse or somebody spend a significant amount of time to inform the individual and be able to get the consent. Clinically, that just would not be possible.

So, what we might be doing, if you impose the same restrictions or the same constraints in both cases, that would stifle the use of these technologies for clinical

purposes. And many people may decide that this is too much of an effort and that, therefore, we should not do whole genome sequencing, and I will do only gene A or gene B, and that would be, I think, detrimental.

DR. GUTMANN: And this is why we have both people who are focused philosophically in astute ways and people who know the practice on the ground -- because if we are going to get recommendations that both move us forward ethically and clinically and scientifically, we have got to take both into account.

DR. WAGNER: Very quickly, Raju, would you correct me? Isn't part of what we want to accomplish with Recommendation 5 to provide an avenue by which clinically-collected whole genome sequencing work can be entered into research use, a research database? Presumably, I guess what you are saying is a clinician would be less inclined to allow that transfer to take place if they are bound by this set of recommendations. Presumably, they wouldn't be bound by this set of recommendations if they are collecting the data simply for clinical use, right, for their patients?

DR. KUCHERLAPATI: So, Jim, traditionally, as you know, in the past much of these records were paper-based records. And therefore, there wasn't really entering the information into any databases, and so on.

As we begin to use more electronic medical records, there is an opportunity to be able to do that. And certainly, active medical centers have begun to accumulate the results. And there are lots of examples where the ability to accumulate those results and analyze them have really provided very significant benefits.

I will just give you one example of that. A few years ago, for example,

when Vioxx was used, it turned out that the ability to look at the accumulated data would have predicted all of the cardiovascular side events that could have been detected. So, clearly, there is a tremendous amount of use, and there is going to be a possibility here.

So, I wasn't addressing precisely whether the physician is going to agree to enter the information into a database, but I was even asking the question whether, if you impose strict limits, whether the physician would even consider ordering a whole genome sequence-based test and might just say, "Let me just look at one or two genes." That means that you are basically sort of looking for your keys under the lights, and that is not what we would like to see.

DR. GUTMANN: So, let me just clarify here, just so nobody is under the misimpression, we are not letting clinicians off the hook. The first recommendation, Recommendation 5, has some significant requirements for clinicians to inform patients of how the data may be used. It is just that the next recommendation goes further with regard to research, purely research-related uses of whole genome sequencing.

DR. WAGNER: But Raj is concerned that the first may be onerous.

DR. GUTMANN: No, I think Raj was okay with the first. He just doesn't want the first to subsume the second for clinicians.

DR. WAGNER: What did you mean, Raju?

DR. GUTMANN: Well, I am trying to interpret, right. Yes.

(Laughter.)

DR. WAGNER: Anything else you would like to say?

(Laughter.)

DR. GUTMANN: Raj, what would you say with regard to clinicians?

DR. KUCHERLAPATI: No, actually, I am thinking about this throughout this discussion/conversation, and I think that the way that it is currently framed, Recommendation 5, leaves it sufficiently vague in terms of exactly what kinds of constraints that we have to put on. That might provide the clinicians adequate amount of leeway to create much simpler consent forms --

DR. GUTMANN: Yes.

DR. KUCHERLAPATI: -- if that is what it required.

And whereas, 6 would specifically state, for research purposes, what the kinds of constraints are.

DR. GUTMANN: And we do say workable consent processes here.

DR. WAGNER: I have got to just follow up for clarification. You are a researcher and you would like my genome. Okay? Would you advise me to go see my doctor, so that he could, with a very brief and much sketchier set of consent processes, enter my data for you as opposed to you collecting it directly, because you would have this more complete requirement?

DR. KUCHERLAPATI: Jim, as a researcher, I need to go to the IRB to be able to access your information, however it comes through. If the IRB would figure it out that I am trying to circumvent the procedure, I would be in serious trouble.

DR. GUTMANN: So, I think this is very helpful. Just let me try to do something very formal.

So, Christine, you suggested we keep them separate. What I suggest,

given the view that if we totally separate these with numbers, the flow isn't clear. There is something very simple we can do with these recommendations.

We have clumped these recommendations under topics. Consent is the topic of three of these. I suggest, under topics, we number recommendations 5A, 5B, 5C. That way, they are under the same thematic topic, but they are separate recommendations. And then, we have discussions under them. I think that works.

Now, Nita, who has been very patient.

DR. FARAHANY: So, I hate to say anything that might be more specific after what Raju just said. But I worry that, with 5A or whatever we are calling it now, that we are dodging some really important questions that have been brought up throughout the process.

So, we heard, for example, early on about BioVU, which is Vanderbilt's DNA data-banking system, where as part of the clinical process you may have blood samples. Whatever is remaining of your blood sample is put into a DNA database, and it is used for research purposes.

And that already, as of 2010, had a hundred thousand samples. There is 500 new samples at least added every day to the system. The mechanism by which it is added is by opt-out rather than by opt-in.

And so, I went through the Vanderbilt a number of times, and each time I went through the system, I didn't even see the form. It is on a computer screen that somebody is actually going through. When you finally get there, they say, do you want to opt-out or opt-in? Because I understood what that was, I said opt-out, please. But it is a

difficult question, one that we heard quite a bit about, which is, are opt-in or opt-out procedures permissible in this context?

And a second issue that we heard a good bit about was reconsent versus consent. And we make mention of that in 6, at least by reference, by saying how the data might be used in the future and explain the degree to which the individual will have control over future data use.

But, given that these are both issues that have been pretty hotly debated in the literature, have come up within our proceedings, I feel like staying silent with respect to them doesn't provide the necessary ethical guidance to some of the most difficult issues that we heard with respect to consent.

So, I would like for us to actually address those issues and to provide some guidance as to both that we think that they are important issues to consider, but also what we think those issues are, whether at the broad level or not. So, in the clinical setting, do we think opt-out is a sufficient basis for consent? Do we think that that actually constitutes consent? Or at the very least, advising that those be important issues that are considered, although I would hope we would do more.

DR. GUTMANN: Yes. So, let me say something about opt-in and opt-out because there is a vast literature. I have read it all, I think.

What we say here in this recommendation would have to be supplemented by what we say in the text. But what we say here implies, I think rightly, that whether you have opt-in or opt-out, you have to inform people of what they are opting-in or opting-out of. So, that is what this recommendation, as it is stated, suggests, that it is not if you have

opt-out proviso, that you have less of an obligation to tell people what they are opting out; the same thing with opt-in.

There is another issue that comes up in the Vandy case which we don't address implicitly here. Although it is not clear that this is the place to address it there, we talk about it earlier, which is what Vanderbilt's system, one of the reasons they think that the opt-out is justifiable is there is a strong de-identification where they have actually done more than simply de-identify. They have scrambled the WGSes, so that it would be particularly hard to re-identify, not impossible, but hard.

Now I think Nita's right; that is something we could discuss in the text. With regard to earlier recommendations, it is less significant about consent than about identification. So, there are some other things we could get into.

But I do think that Recommendation 5A -- it won't even be 5 now because the other ones will be clumped, too -- but I think it covers -- it basically says, and this is a question of whether you agree, that whether you have opt-in or opt-out, you still have the requirement of explaining to people what they are consenting to.

DR. FARAHANY: I agree with that completely. Under any approach, we would want somebody to be clearly informed of their options.

DR. GUTMANN: Yes.

DR. FARAHANY: But, as you know from literature, it is characterized as a consent issue, right, which is whether or not it is meaningful for the same kind of consent to opt-out, even when clearly explained your options.

And so, one of the reasons that Vanderbilt said is they strongly de-identify.

So, they have increased security measures. But they also said it was because the rate at which people entered their data into the database was significantly higher in an opt-out process than an opt-in process.

DR. GUTMANN: Right.

DR. FARAHANY: And so, it was the utilitarian benefit of actually having far more people have their data in the database, and not because necessarily they clearly understood, right, but because it is more difficult to say, "I will opt-out," and the presumption is that you are in unless you ask to be out. And so, I think that does present a separate issue that I would hope that we would address.

DR. GUTMANN: Right. I am not a utilitarian, and that doesn't mean that consequentialist considerations -- non-utilitarians believe, by definition, that not only consequences count, but consequences count, too.

Having read that literature and thought about this a lot, I don't see that there is any moral imperative to have an opt-in rather than an opt-out procedure, as long as you inform people clearly about it and don't use it as a way of getting around fully-informed consent.

DR. WAGNER: Are people saying that?

DR. GUTMANN: I don't know. I am speaking for myself, not the Commission here. What I would not want to see, and what we could say in the text, is the use is opt-out as a way of getting around fully informing people about what they are agreeing to.

And making it easier or harder to get people to agree to something that is

for the public good, as long as they are being asked to consent to it, is consistent with what we are saying in the report, that we want the public good to be served, to try to find ways in which people are more likely consistent with informed consent to do something that is for the public good.

Now people who are purely fearful of these processes might say, "Wait a second. That makes it too easy." And I would worry about that if we were harming people.

Yes?

DR. FARAHANY: The problem is, I mean, part of that --

DR. GUTMANN: As somebody who did opt-out -- I mean, this might be an irony because I being on record as not being utilitarian, we might have the utilitarian who doesn't like the opt-out position.

DR. FARAHANY: I do not claim to be utilitarian.

DR. GUTMANN: I don't know, but --

DR. FARAHANY: So, I am not as comfortable with just fully-informed consent -- or, no, fully informing somebody and saying that opt-in or opt-out is exactly the same with respect to consent. I think that the evidence shows the people don't fully understand, even when given the information about opt-out, what it actually means. Because the default rule sets it up so that their information goes into a database, I am concerned about it.

So, now the irony here, I thought you were going to say, is that, as the person who is less concerned about privacy of access --

DR. GUTMANN: Yes, yes, yes.

DR. FARAHANY: -- right, that is the part that is a little ironic. And yet, I do think people should have the opportunity to choose. And I don't think that it is as meaningful of a choice as to whether or not their information flows when it is opt-out as opposed to opt-in.

DR. GUTMANN: Okay. I mean, I am not speaking personally now, but just logically, philosophically, you will find that people who have to opt-in don't understand fully, either. So, that logically doesn't tell one way or the other. And it is only, I think, logically, if you think there is some harm in this to people that we need to protect them from by making it harder psychologically for them to agree to it.

And since that would suggest other barriers besides the opt-in/opt-out, I think it is a logical mistake to think that there is some morally greater barrier to people opting-out to them opting-in in this particular case. When there is harm involved, it is a different story.

Dan?

DR. SULMASY: No, I think, as has been stated, that if it is now going to be 5A, then under 5A we need to have a pretty robust discussion of several of these overriding issues. So, one of these is the opt-in/opt-out question, and I don't know that we are going to achieve consensus in the next 10 minutes on this, but at least we know we need to discuss that.

I think the consent/reconsent issue is another one. And then, as Raju has suggested and John had raised yesterday, the question of what we mean by consent, a more robust consent in the clinical setting, also needs to be discussed.

This is not as if there isn't already a gradation, Raju, as you know, in the discussion of informed consent for various clinical procedures. What we don't want, I think, is something to say, "This is just a blood test," the way it would be for a CBC. But, yet, we don't want to go to 20-page consent forms. It may be something that is more like the discussion that ought to take place before doing simple genetic testing like doing BRCA1 testing or something like that.

We need to have that discussion as well, so that it isn't just the vague recommendation, but something with more teeth. That should be in the body, I think.

DR. GUTMANN: John?

DR. ARRAS: Yes, I think I am prepared to sign on to the sort of analysis of opt-in and opt-out that you just offered, Amy. But I want to affirm the importance of the kind of issue that Nita is raising here. Because it goes to the question of how complete our analysis of informed consent is going to be.

Nita is noting here that informed consent has to do not just with the amount of information that people receive. It has to do with the quality of the choice that they make. Informed consent has to do with choosing, right?

So, if we just limit ourselves to the issue of information, we are not going to give a complete analysis of consent. I do think that we should have a full-blown discussion, giving the staff more homework, on this issue of opt-in versus opt-out, the kinds of issues that Dan is raising. I think this is really important.

DR. GUTMANN: Yes, yes. Sure, go ahead.

DR. KUCHERLAPATI: I think there is something that I am not making a

recommendation, but just information-wise. All of the people in Iceland, there was an effort to try to obtain DNA and to be able to do DNA-based analysis.

And so, in that particular case, essentially, the whole population of the country, they only had the opt-out option. So, the default was to allow their DNA to be analyzed unless they specifically asked, said that "I don't want to be included," just for information.

DR. GUTMANN: Barbara?

DR. ATKINSON: I was just going to say that I think that opt-in and opt-out is really used in a clinical setting for everybody's clinical records for all of them. And we talked about the uses from that.

If we are going to limit it in some way or even discuss limiting it, I would only limit it to those genome kind of studies and maybe say that they are different. But I am not even sure I want to go there.

So, I just want to come down pretty much in favor of discussing it in our discussion, but leaving it open. Because I can tell you, with electronic medical records, as we have already heard, it is going to be very important to aggregate the most data possible from the most places. And that is what people are really moving toward, to get into big databases. And I don't want to see it limited.

DR. GUTMANN: We have in the briefing books articles, and there are more if you want, but there are some really good articles that discuss, among other things, the Vanderbilt case. You should all read it because, if it is the case, whether it is Iceland or Vanderbilt, if we recommend against opt-out, we are basically invalidating a whole set of

procedures.

Now that doesn't mean we couldn't ensure that, whether it is opt-in or opt-out, it is as fully informed as informed consent can be, which is never fully on these complicated things. It just isn't. And it is real choice, that people aren't pressured in some ways into opting-in or opting-out.

Christine? Oh, Anita is next. Thank you.

DR. ALLEN: Thank you.

First of all, the Icelandic DNA project was incredibly controversial among bioethicists. It wasn't as if everyone just said, "Oh, that's great," because everyone is opting -- anyway, it was controversial.

(Laughter.)

But what I really want to say is I always think about these questions about what we should do in this context and the broader context of privacy law and policy. It is interesting to me that in the European Union, when it comes to all types of sensitive data, opting-in is the norm. That is the law. The European Union is held to an opt-in approach.

DR. GUTMANN: And they are doing so well, too.

(Laughter.)

DR. ALLEN: Right, but it is because the quality of choice issue is one, but the nature of the data issue is privacy is seen as a human right. Sensitive data is very important. It is too important to have the business sector have the advantage over the citizen.

So, in the U.S. we typically do go with opt-out regimes. It makes it easier

on the business sector. It makes it more convenient. And it may not be wrong. In fact, some courts have found that you constitutionally cannot require people to have to opt-in.

So, we have this like sort of ideological/philosophical kind of split in sort of the geopolitical context, but also in a sort of philosophical context. I totally respect, Amy, your analysis that it doesn't make a difference as long as people are informed about the things.

But we do sort of know that, as a practical matter, people do tend to go along with things when it is more you have an opt-out. And we also know that the nature of data does matter.

So, I am not opposed to you approach, but I do think we should understand that it is not a trivial -- I mean, I am not saying you think it is a trivial.

DR. GUTMANN: No, I don't.

DR. ALLEN: I mean, it is really a huge choice we are making, we as a country are making, if we prefer and go with an approach which says that people should be informed, and then we should be informed in opt-out --

DR. GUTMANN: So, let me just be clear.

DR. ALLEN: Yes.

DR. GUTMANN: I am not recommending --

DR. ALLEN: Yes.

DR. GUTMANN: -- that all schemes be opt-out schemes.

DR. ALLEN: Yes.

DR. GUTMANN: I am simply saying that, morally and logically-

speaking, when it comes to things that are not directly harmful to people, so we are not pushing them into harm, there is no moral or logical difference --

DR. ALLEN: Yes.

DR. GUTMANN: -- between opt-in and opt-out.

DR. ALLEN: And what I am suggesting, Amy --

DR. GUTMANN: In both cases, you need to inform people about what their choices are and you need to give them a choice.

DR. ALLEN: But someone might argue that the nature of the information, that certain data, whether it is financially-sensitive or medically-sensitive or genomically-sensitive, is such that the harm is intrinsic to the nature of the data. And so, we are not torturing them. We are not causing them pain.

DR. GUTMANN: No.

DR. ALLEN: But there is something about the nature of the data that calls for perhaps a higher or different approach. That is all I want to say.

DR. GUTMANN: Yes. No, I understand.

DR. ALLEN: Yes, yes.

DR. GUTMANN: And I am not willing to take that step to say that the data is such that it is intrinsically-harmful, and therefore, we need to put this protective barrier.

I think if we want as a Commission to go that route, we had better have a deliberation about all of the language of the public good that is being done by whole genome sequencing potentially. And I think I would stand behind that from everything that

I know.

Okay. I am going to make a decision to move on to the next recommendation. I am sure things will come up, but we have three more recommendations to go. I think it is important to get through them.

Recommendation 5C, we will call it now, okay, and it is still under the consent rubric. So, we still have opportunities to talk about some of these really important issues.

And let me just say, before we go on, that everything that we have discussed here needs to be put, if not in the text of the recommendation, because we want to keep the recommendations reasonably succinct, in the body of our report, so we come to terms with some of these important issues in ways that you can't do just in recommendations.

5C, "Funders of genomic research should support studies to evaluate proposed frameworks for return of incidental findings and other research results derived from whole genome sequencing and investigate the related preferences and expectations of the individuals contributing samples and data to genomic research and undergoing genomic sequencing in the context of clinical care or direct to consumers." So, this is about incidental findings.

Jim, go. And then, Nita, go. We have time for both. Go.

DR. WAGNER: Okay. I want to make sure that the intent of the Commission is, again, reflected in this. It seems to me by a recommendation that some other group or a set of groups should support studies to evaluate this position in the

incidental findings is to say that we would be comfortable or that we have, at this early stage of considering this, no guidance from the bioethics perspective.

My own kind of thinking on this -- and the reason I would look to Nita on this, she and I have had a telephone conversation about this. I think she has even sharper issues with this. But I wonder about such things as recommending at the very least whom we imagine is best positioned from a bioethics point of view to receive incidental findings.

For example, is it really the subject, is it really the individual that should receive that? Should we have health workers receive that? Certainly, when I have a blood test, Dan, as you suggested, if there is an incidental finding in there, I don't get a phone call or an email from the blood lab. That goes to my clinician. I realize my clinician ordered the study in the first place, but, presumably, that is a good thing to do anyway because of my inability to interpret what that incidental finding might mean.

I offer that as a suggestion, as one way at least to offer an opinion about what we think the route for incidental findings ought to be, about which I think we are silent right now. And I am a little uncomfortable with that.

DR. GUTMANN: Nita?

DR. FARAHANY: Thanks, Jim. I think that is a helpful addition.

So, I talked to Jim about this recommendation as well as a couple of other ones. What is notable about a couple of the recommendations I have spoken to, I think, is that we are taking a much softer position in this report than we have in some other reports in terms of providing, I think, specific guidance. And that can be the right approach for a number of issues, given how each of these issues really could be an independent study.

So, incidental findings is an enormous debate in the literature right now with respect to genomic information and other types of research that are happening. It is especially thorny in something like whole genome sequencing where we simply wouldn't expect necessarily a person who is collecting a whole genome sequence to have the knowledge, expertise, or ability to be able to go through the entire genome and search for things utterly unrelated to their research and be expected or have a duty to return incidental findings.

And yet, some people believe otherwise. Some people believe, if you take on the data, that you have a duty to search even outside of your expertise. And if you were to come across something that might be incidental, even if it is outside of your area of expertise, that you would have a duty to report it.

Given that there really is this robust debate that is happening on this issue, given that we are taking on whole genome sequencing, and this is one of the thorniest issues in it, I think we need to provide some more specific guidance. And to the extent that we actually have any value to provide besides that we think somebody else should take a look at it, I would like for us to do so, to provide what are some of the issues at least that we have uncovered with respect to incidental findings as we have gone through the process. What are some of our initial intuitions about this subject that we think might guide individuals as they do this research?

DR. GUTMANN: Good.

Christine?

DR. GRADY: I actually agree with Nita. I mean, it is still a very hot topic

in the community of people who think about these issues. But there have been several consensus documents and consensus meetings and some guidance that is already out there.

And we heard a lot about it from some of our people who gave testimony, including Dr. Knoppers yesterday. You know, there are these bins, there are these general…. I think adopting one of those, as this makes sense to us from an ethical perspective, would be a very good thing to do.

DR. GUTMANN: Raju?

DR. KUCHERLAPATI: I think, indeed, there is a very significant amount of debate about this issue. But from the Commission's point of view, I think, actually, it can be distilled into simple things that we have considered in other reports. We might be able to make a recommendation.

And that is that there are some people who argue that incidental findings, unless they are immediately actionable, should not be reported back to the patient or individual. Other people say, how could any researcher or a physician or a clinician, without really a complete adequate amount of knowledge, be able to make such a decision? Rather, the decision should really rest with the individual who is providing the material to be able to do that.

And so, it is basically a way to look at that is the supremacy of the investigator or the physician versus the individual, and I think it may be possible to actually come to, based upon the ethical principles that we have been utilizing, to come to a conclusion about that.

DR. GUTMANN: John?

DR. ARRAS: I have got a comment about the geography of this particular recommendation. I am not sure I understand why this goes under the heading of informed consent.

DR. GUTMANN: Okay. Let me explain why this should and why all of it shouldn't come under informed consent.

So, right here under consent, there should be a statement by the Commission about why individuals should know what they are consenting to --

DR. ARRAS: Yes, yes.

DR. GUTMANN: -- with regard to the return of --

DR. ARRAS: Right.

DR. GUTMANN: -- incidental findings.

DR. ARRAS: Yes.

DR. GUTMANN: And so, that is what this should say.

What John is pointing out, and I think the other comments all are focused on, is whether we, as a Commission, will take a stand on what incidental findings should or should not there be an obligation on the part of researchers or clinicians to return and why.

DR. ARRAS: Exactly.

DR. GUTMANN: And that isn't a matter of informed consent.

DR. ARRAS: Yes. In other words, the substantive issue is not an issue of consent.

DR. GUTMANN: But there is a place here --

DR. ARRAS: There is a part of it, yes.

DR. GUTMANN: And I think implied by 5A and B is a recommendation that individuals be informed as to what incidental findings, what is the scope of incidental findings that will or will not be returned.

DR. ARRAS: I agree, yes.

DR. GUTMANN: Whether to them or to a clinician or a doctor.

DR. ARRAS: Yes. I just think that it is important to note that it is not just an issue of consent. That is why I have doubts about whether this entire discussion should take place under the rubric of consent.

DR. GUTMANN: Yes.

DR. ARRAS: Because, look, I mean, it is true --

DR. GUTMANN: Correct.

DR. ARRAS: -- that people should get information about all the aspects of the study. This issue, the substantive issue here really comes into the domain of like research design, or whatever you want to call that, just as privacy would. Okay?

So, people should be informed about what to expect during the study, what will be returned. But the substantive issue is not an issue of consent.

DR. KUCHERLAPATI: May I?

DR. GUTMANN: You may.

DR. KUCHERLAPATI: I think it is entirely an issue of consent. Some people argue that whether or not the incident -- whenever you do whole genome sequencing, you are going to find a number of things that would be considered to be incidental. And the question is: what are the circumstances under which you would provide

that information back to the individual who provided the DNA sample? And some people argue that the individual should make the decision at the beginning whether they would want to receive such information or whether they do not want to receive such information. If that is the case, then it is purely a consent issue and not anything else.

DR. ARRAS: Could I just respectfully disagree?

I followed that reasoning, and that is why I think is, in part, an issue of consent. Okay? But another way to look at this, Raju, is to view it as a question of what obligations fall on the shoulders of researchers.

If they have information that is actionable, that is important for a patient's health, one could argue that the pivotal question is what are their obligations to patients, and that is not reducible to consent.

DR. GUTMANN: Dan?

DR. SULMASY: With respect just to the question of whether to return findings to the individual or clinician, I think we have to bear in mind the fact that many of these studies will be long-term studies going on for a long time. The duration of clinician/patient relationships in the United States is getting shorter and shorter. And so that the ideal of being able to return the results to the clinician may not be practicable, even if it is five or ten years down the line. So, I think we need to keep those sorts of things in --

DR. GUTMANN: When we took on the whole genome sequencing, we agreed of a focus on issues of privacy and the public good. We can decide to broaden it to the issue of the return of incidental findings. But, other than consent, which it is an issue of consent, we are all agreed to, the actual decisions about what incidental findings should be

returned to whom is actually beyond the scope that we had originally said we were going to do in this report, in part because we recognize, as everybody here recognizes, that there are a large number of controversial and important issues that you can't take on in one report without making it more voluminous and lengthy in duration, as well as in length in the physical product, than we had set out to do.

So, I think we should flag this as an unresolved issue beyond the consent issue on obligations of researchers. Because I think most of us, if not all of us, are pretty knowledgeable about the issues out there, but simply our time constraints and the scope of this report, we didn't set out to do that particular issue.

Barbara?

DR. ATKINSON: And for just that reason, I sort of like leaving the recommendation in and leaving it as vague as it is, and saying it needs more study. I don't think we are ready to be more specific about it. I would hate to see something not here about it at all, but this really suggests that we need more work on the issue. And I think that is exactly where we are on it.

DR. GUTMANN: Although I think it could be reworded, because I think it suggests that the recommendation is more study, as opposed to the recommendation that people be fully informed about what the status of the return of incidental findings is. Socratic wisdom being knowing what you don't know, at this time, we can say on the substantive issue of when and what incidental findings should be returned to whom, because there is a big question, as Jim said, as to whether it should be returned to the individual or to a clinician, we would propose that -- and we can point to some of the consensus studies out

there, which are good starting points, but they need to be brought further to more specific conclusions than we are prepared to do in this report.

Nelson?

DR. MICHAEL: Yes, I think a compromise, it could actually go into the recommendation, as I think Nita is probably suggesting, continuing the theme of suggesting what another Commissioner is thinking without actually asking her.

(Laughter.)

DR. GUTMANN: We have been pretty good so far.

(Laughter.)

DR. MICHAEL: No, no, I think we have been pretty good.

Or it could go into some of the supporting text around it. But I think I was struck by Bartha's comments yesterday of providing sort of the three stools of scientific and clinical validity, which are changing over time, as well as actionability, if that is actually a word. I think that is the one that she used.

I thought that was very helpful for me; that particular theme was very useful because we understand that the science of genomics is constantly changing, and especially some of the multigenic haplotypes that right now we don't understand, are not smart enough to understand how those work, discovering rarer and rarer alleles that sum together as multigenic haplotypes could, in fact be informative. We just haven't collected enough genomes yet to know those sort of things.

So, some of the things that right now aren't valid, either scientifically or clinically, and therefore, aren't actionable, could be in the future. So, I think we get into the

real problem of how granular we are going to get if we really attack this issue. But maybe, again, the compromise would be we touch on one of those bins that Bartha mentioned yesterday. I liked particularly that one, and that might provide enough of a bridge.

DR. KUCHERLAPATI: May I make a very brief illustration?

DR. GUTMANN: Yes.

DR. KUCHERLAPATI: This is just for Dan's sake. Thank you.

Dan, to comment, I think you are right about there are certain kinds of things that are going to take a long time for understanding. But, you know, a concrete example today -- and we have heard something about this yesterday -- is that when you sequence the whole genome, for example, you would be able to look at the status of ApoE4, and an individual who was homozygous for this ApoE4 allele would have a 70-percent chance of developing Alzheimer's by the time they reached a particular age.

The question is, should you reveal that information to the individual or not? And Watson had his DNA sequenced, he said you could make all of the information available publicly except this region of ApoE4. And so, the people had to respect his wish and delete that information, and put the rest of the stuff on the internet.

And again, the people debating as to whether finding out one's ApoE4 status is helpful or not helpful. Some people argue that it is not helpful. Other people publicly argued, no, I would actually be able to do something about that. The way that I would deal with lifestyle or how I would exercise, mental exercises, and so on and so forth, would be completely different.

DR. GUTMANN: That is why I have used that example of early-onset

Alzheimer's because there is no agreement among morally-astute, reasonable people as to whether they would want it, about whether it is actionable. It is certainly not actionable in any clinical sense at this point, but it may be. So, there is an enormous amount of research going on.

But, under the immediately-actionable category, which is the only category I think that there is some compelling argument at this point for return -- I mean, there are arguments on both sides on other things -- this one is the most wrenching. I think if you do a case study of focusing on the controversy that exists now, this is the exact right example to use.

I am going to ask Steve -- yes?

DR. HAUSER: So, I was just thinking about what we mean by actionable. Whenever that word is mentioned, I think it is a vague term. And you have made that more clear --

DR. GUTMANN: Right.

DR. HAUSER: -- when you said "immediately actionable".

So, one could argue for the Alzheimer's example that the lifestyle adjustments that are marginally helpful are adjustments that we all should make, independent of knowledge of ApoE status.

What about all of the pharmacogenomic information that are not immediately actionable, but might pinpoint a variant that could put somebody at risk and at high, very high risk for a terrible side effect from a drug? That is not immediately actionable, but it is potentially important to the person. Immediately actionable might be a

tumor-associated gene.

DR. GUTMANN: Right, right, right.

And again, this is not directly -- I just want to make clear -- this is not directly on the subject of privacy, confidentiality, the public good. It is a broadening of -- it is fascinating.

DR. WAGNER: Put me on your list, when you get time.

DR. GUTMANN: Yes, right.

On the early-onset Alzheimer's, it is the case, you know, factually-speaking, that some people really want that information and would want to act on it, and other people feel it would destroy them to know it and they would rather not have it.

And so, we need, as a Commission, to recognize that there are some cases where the kind of information that exists and the ability to treat it medically, or the inability, really does significantly divide the population of reasonable, not-inherently-fearful people into different camps. And this, I think, a whole book on the subject is in order.

Christine? And then, Jim.

DR. GRADY: I think maybe you have convinced me that we need to focus on consent and recognize the work that has been done and the difficulty with the controversies over what is actionable and what is immediately actionable.

But I think the frameworks that have been developed that divide things into, you know, you should offer, you can offer, and you shouldn't offer, those are useful frameworks.

DR. GUTMANN: Yes.

DR. GRADY: But maybe our recommendation, if it is going to focus on consent, can deal with the question of, is it all up to the person whose data we are collecting? And I think the answer, I guess my view would be, in not every case is that correct. In other words, depending on the circumstances, depending on what you are testing for, research or clinical care, et cetera, and recognizing the various preferences of people that we know people have --

DR. GUTMANN: Yes.

DR. GRADY: -- and the potential consequences of receiving information, that we should at least recognize that in some cases spelling out what will be done is important, but it is not always up to the person who is consenting. They can say, "No, I don't want to do it."

DR. GUTMANN: Absolutely. Absolutely.

Jim?

DR. WAGNER: I would like to suggest that we do come up with just two or three foundational -- we are a bioethics panel. We did say that we wanted to address, we are going to be addressing the ethical issues of whole genome sequencing. I think it is fair to say that the scope of our work is such that this is not a thorough piece.

But it seems to me there are a couple of fundamental things that would be wrong not to talk about. One was brought up earlier. I don't know how the rest of the Commission believes, but I do think there is a concern that we haven't talked about yet, maybe we have talked about it briefly, that I think is a principle that says the discovery of such findings it not the burden of the researcher. You don't expect the researcher to go

looking for things.

I have a concern that if my genome had been sequenced and at 75 I am discovered, or 65, to have Alzheimer's owing to being homozygous for ApoE4, that I could go to your database and say, "You should have known this." I think one principle is we don't expect that to be a burden of the researcher.

I think another principle is, however, that in my own view it's wrong not to report the availability of this discovery when it is discovered incidentally.

DR. GUTMANN: Let me just, I want you to keep going, but it is not a burden of the researcher is No. 1.

DR. WAGNER: You folks can say it better than I.

DR. GUTMANN: And No. 2 is --

DR. WAGNER: No. 2 is that the availability of an incidental finding, it seems to me it is ethical to report, not what the finding is. In other words --

DR. GUTMANN: An actionable one?

DR. WAGNER: Exactly right. You tip it off so the individual can make that decision, just like Watson, of whether or not he wants to know what it is.

DR. GUTMANN: I am really trying to understand, my job is to understand what that means.

DR. WAGNER: They are two sides of the same coin. One is that, if I am the researcher, I don't have to go teasing through everything. I don't have an assumed burden to look for all the possible things that I could discover that are incidental to my study.

And the second is, if in doing my study I incidentally discover something, do I have -- maybe I should ask it this way rather than having already voiced my opinion -- do I have an obligation to let the individual know that the results of that discovery are available?

They are two sides of the --

DR. SULMASY: Just quickly, from a clinical point of view, that has got to be prospective and really can't be retrospective without already letting the person know what the result is. We are calling you up to say, you know, "We have a result here. Would you want to know?"

DR. WAGNER: Exactly. That is what I want to debate. I don't think it is quite --

DR. GUTMANN: Yes, but --

DR. WAGNER: Let me give an example.

DR. GUTMANN: Okay.

DR. WAGNER: Our neuroimaging folks, your neuroimaging folks are doing some work, and they discover an anomaly. And I wonder if they don't have an obligation in that process. They were actually looking for blood-flow studies. They were doing some sort of cognitive study in the brain, but they discover an anomaly.

Do I have, do they have, a responsibility to say, "We have discovered an anomaly?" and for you to say, "Well, tell me what it is," or not? Is it a tumor? Is it a structural anomaly? Do you see the --

DR. FARAHANY: Can I speak?

DR. GUTMANN: Yes.

DR. FARAHANY: So, especially in neuroimaging, this has come up quite a bit. The problem is many, but one major problem in this area is many times the person who is doing the research in neuroimaging is a technician who is very limited in their knowledge about other types of things. What they might see is something that might be clinically-relevant.

And so, how some of them have dealt with it is through the process of consent, which is they have included -- you know, you can include your physician's information as part of your signing-up and consent process. And you can say, if there is something that may be clinically-relevant, I would like it or I would not like it disclosed to my physician.

It is then sent to your physician, and then your physician can notify you if it is something clinically-relevant. So, the obligation, then, is part of the consent process, and the obligation, then, is not to go searching for anything. It is only if you come across something that you may know, but it doesn't put a greater burden on the researcher to actually know what that means.

DR. WAGNER: Exactly, exactly. That actually was linked to my earlier comment that I wondered about returning data directly to the individual as opposed to a clinician, yes.

DR. GUTMANN: Raju?

DR. KUCHERLAPATI: There is a very practical aspect that we are not considering. That is the following: at the present time, no research data on genome

sequencing can be reported back to the individual because most of those things are not done in a CLIA lab. Absolutely not, they cannot be done.

The only way that clinical results can be reported, the results can be reported back to the individual, is if the test is done in a CLIA lab. Unless we change, a law changes, that is the way it is today.

So, when you talk about reporting incidental results, it is only relevant for clinical purposes. That is when the tests will be done in a CLIA lab, and the results will be obtained, and you have to think about returning results back to the individual.

So, I just wanted to make sure that we don't mix up these two issues.

DR. GUTMANN: Yes.

Christine? And then, I am moving on because there is a very practical consideration of time here.

So, go ahead.

DR. GRADY: Well, I was just going to respond to Jim's question because I think that is what John was referring to. That is the question of what is the obligation of the person who is obtaining the sample.

That is why the people who have worked on this have divided things into clinically-valid, scientifically-valid, and actionable as guideposts for how you decide what you should return and what you can return, and what you shouldn't return to participants.

But it is a huge body of literature, and it is complicated because each of those decisions is value-laden.

DR. WAGNER: Besides a Commission on Bioethical Issues, what other

groups should opine on the bioethics of this?

DR. GUTMANN: There are some significant reports out there. I think you are absolutely right; a bioethics commission should. But if we are going to get a report out on everything that we have actually spent four meetings deliberating about and on, we ought to be, I think, wise enough to recognize that we are not going to be able to thoroughly vet the issue of incidental findings.

We have something clear to say about consent. We have something that we can say about the very good consensus documents that are out there on incidental findings and the kinds of distinctions they make, which I think we all agree are important distinctions to make. And we can say a lot more than is in this 5C, in the text.

But we are not going to have, I mean, I think it would be unwise for us to think that we could do in a detailed fashion everything that needs to be done about incidental findings.

DR. WAGNER: I don't think we could do everything. I am happy to go with the consensus of the group.

I am concerned that, because this is called incidental findings, we imagine it to be incidental among all the range of bioethical issues associated with whole genome sequencing, when, in fact, I think it is one of the biggest issues.

DR. FARAHANY: I agree with you, Jim.

DR. GUTMANN: Well, I mean, if people want to postpone the report and expand it, we can do that. I know the staff is sighing, but it is an important issue. I mean, I think a number of us know the literature quite well, but we can't possibly cover it beyond

what has been done in the literature and the reports out there in the time between now and September 17th, when we expect to do it. And we won't do justice to it, and if we are going to do it in any thorough way, we need more time to do it.

DR. KUCHERLAPATI: Very briefly about this?

DR. GUTMANN: Yes.

DR. KUCHERLAPATI: So, Jim, the issue about these incidental findings is that whether revealing such information would harm or whether it would violate any of the ethical principles, the only way to really find out is to actually study and to have an adequate number of people enrolled in a study where you would be able to provide this information or not provide the information and study it.

And actually, there are such efforts currently underway. There is a big consortium right now of different investigators from around the country who are studying exactly this issue. I think the results of that will be available in maybe two or three years. I think we would be able to come to a conclusion more. I don't think we are quite ready to be able to make a recommendation and say we have got to go this way or this way.

DR. GUTMANN: I am going to make the decision, because of time, that we are going to move on to the two more recommendations, which are about oversight.

DR. FARAHANY: Can I just ask a question of you? You said it is possible that we could delay, if it was important to the Commission, to take up this issue. Is it worth seeing if that is something the Commission would want to do, given that some people think it is one of the most important issues to take on?

DR. GUTMANN: I think after this meeting we can see whether there is --

I mean, I think that is something that we can just see whether a majority of the members of the Commission want to delay the report and expand it considerably or want to issue this report with the possibility of going back and issuing a separate report on incidental findings in the future, recognizing -- I mean, I am just being very practical -- if we do delay this report, it means that we will also delay the neuroimaging report. There are only so many of us.

And so, we will move on to medical countermeasures for children and get that out at the end of the year, and we will just postpone the issuing of this report, which we have the freedom to do, and it will be a bigger report.

I am willing, more than willing, I am happy to go with the sense of the Commission. I would say that, given the culture we live in, shorter reports get read more. You know, they just get digested. So, my own bias would be to get this report out, say something about what we do and don't know about incidental findings, and then reserve to us the possibility of coming back and doing a report on incidental findings. But I am happy to go either way.

DR. SULMASY: Yes, it actually may be the case that, since the issues overlap, this issue of incidental findings overlaps with neuroimaging, that it could be something we take up greater detail when we do a report on neuroimaging, yes.

DR. GUTMANN: Yes. Let's move on to this, so we get through. And then, we can just decide on that.

It has been, by the way, in every report, just for everyone to know, in every report we have done we have had to decide where we draw the line between what we will

feel that we have the time and the capacity to opine on, and this is no different in this regard.

Recommendation 8, this is on oversight now. "Funders of genomic research and relevant clinical entities should facilitate explicit exchange of information between genomic researchers and clinicians while maintaining data protection safeguards, so that genomic and health data can be shared to advance genomic medicine." We had a significant discussion of this and presenters on how important this is.

Does anyone want to say anything about this recommendation? I think this recommendation we agree with and we have a lot of supporting evidence.

Nelson?

DR. MICHAEL: Yes, I don't feel strongly about this, but I wonder if we should also include the commercial sector here or not.

DR. GUTMANN: Yes. I think that is a good idea. Anyone disagree with that?

DR. KUCHERLAPATI: I don't think you can force the commercial entities to introduce --

DR. GUTMANN: Saying facilitate.

DR. MICHAEL: We can't force anybody. We are an advisory board.

DR. GUTMANN: We have the text here. It says "facilitate".

DR. MICHAEL: We are just moral authority only.

DR. GUTMANN: Okay. Recommendation 9, "Policymakers should avoid restrictive rules that proffer few benefits and hinder progress in genomic research." This is our regulatory parsimony, which, while it sounds like whatever the contemporary

equivalent to motherhood and apple pie, it, I think, doesn't go without saying, given how regulatory rules have expanded.

The second sentence, "Further, policymakers should accommodate ample opportunities for the exploration of alternative models of the relationship between those enrolled in research and the researcher, including participatory models."

Open for discussion. We are okay on that?

(No response.)

I have one other possible recommendation that I want to suggest that we don't have a draft of. But if anyone has any more on this, I am happy. I think we have had a thorough discussion of this.

But, Raju, go ahead.

DR. KUCHERLAPATI: I just want to make a comment, and that is that, during all of this period of time and human subjects or materials from human subjects have been used for research, it was always considered that the individual who is providing the materials or information is like a donor of information.

DR. GUTMANN: Yes.

DR. KUCHERLAPATI: And there is this other group that is going to take that information, and they know better how to use that information.

I think one of the things that is emerging, and I think we had several witnesses who really dealt with this issue, and said that we should be thinking more as a partnership between the investigators and the participants, and that type of participatory model, it is truly a participatory model and partnership model, that many of these types of

issues that we talked about might be well resolved.

And I don't know whether the Commission would agree with such a view, and if it is, whether we should try to encourage such, to move towards such a model where there is a partnership between the patients and the investigators rather than a passive role that the patients currently have.

DR. WAGNER: Let me comment on that. Raju, I agree with you very strongly, actually. It gets back, also, to the possibility for us to be a little more precise in language. I agree with you that I think donors donating tissue, donating whatever it is, also donate and give up certain rights of exercise over that.

In fact, the same is true in fundraising, right? If you are donor, you can't get your IRS tax exemption if you continue to exercise authority over the use of those.

Partnership implies the other, that there is some continuing connection. I don't know how, if the item we are talking about is the whole genome, you can truly be just a donor, because the difficulty of separating your identity from it is extraordinary relative to other sorts of things.

So, I think it would be very good language to use, a very good thought process to understand that there is this ongoing relationship between the individual and the material that has been given for study that is different from a donation.

DR. GUTMANN: A lot of the literature has talked about collaborative relationships where there is a back-and-forth. Partnerships have a kind of legal meaning which are not strictly speaking true in any particular case, both in the sense that the researcher isn't a partner to the person, and the person isn't a partner in all the research. But

there is in the participatory models -- and we have heard some of them in earlier sessions -- there is an ongoing collaborative relationship. That is what this recommendation, which once we flesh-out in the text, is meant, as Raju, I think -- it has many benefits.

DR. WAGNER: "Participant" is a good word.

DR. GUTMANN: Participant, yes.

DR. WAGNER: Better than partners.

DR. GUTMANN: Yes, yes, yes.

DR. WAGNER: So, participant versus --

DR. GUTMANN: Yes. So, let me suggest another possible recommendation, which in some sense provides, I think, a nice set of bookends to this study. Because we begin the study by saying it is really important to tackle issues of confidentiality, privacy, control with regard to whole genome sequencing because there is a real public good to be gotten from the science being able to move forward on it.

And a whole set of our recommendations are about protections of confidentiality, privacy, consent, and so on. It would be nice, I think, to have a final recommendation that encouraged the federal government to facilitate access to the social benefits of whole genome sequencing to the broadest-possible number of individuals who could benefit from it.

Because that, in a sense, makes good in our recommendations the promise that there is public benefit here, and that is why we want to ensure privacy/informed-consent, to enable this to happen. That is why we want regulatory parsimony, and so on.

There is another reason to have such a recommendation of the federal

government facilitating the broadest feasible public use of the results. The federal government funded whole genome sequencing. We have now an Affordable Care Act which has been deemed constitutional, and there will be ongoing regulatory/policy decisions made as to who has access to what forms of medical treatment and clinical practice.

So, I think it would be good for us in a broad way, but with clear ethical grounding because this was funded by the government, and it promises public good, to recommend that the federal government do what is in its power to facilitate access to the goods of whole genome sequencing.

Dan?

DR. SULMASY: I would very much support that. I think it reflects our final principle of justice in terms of those, and we ought to make sure that we make reference in the recommendation to that principle of justice in the distribution, which I think you are implying.

DR. GUTMANN: Yes.

DR. SULMASY: But make it explicit.

DR. GUTMANN: Yes. So, it refers back to our principles of justice, to public beneficence, and, also, frankly, to reciprocity. If the government funds something in the public good, it ought to carry through to the extent possible to ensure that it can be delivered on the public good.

I know, Steve, you had something you wanted to --

DR. HAUSER: Yes. Some of this is reviewed in one of our handouts by Burchard and Bustamante. But, in the most recent whole genome association era, I think

that the overwhelming numbers of studies and samples utilized on the research side were from individuals of European descent. And obviously, because of differences in the genetic architecture of non-Europeans compared with Europeans, this means that the benefits of that research will not translate into clinical benefits as quickly for non-Europeans. And we should have a recommendation that helps ensure that this is less likely to happen in the whole genome sequencing era.

DR. GUTMANN: Good. And that is a way of in the text being specific about why this recommendation actually has some bite. There are some specific issues about who can benefit here, and government can make a difference.

I have Anita and John on my list.

DR. ALLEN: Amy, I think you are absolutely right that we need this recommendation. I think it is right that we need it both because it is a matter of justice for all and, also, a matter of reciprocity. I mean, the American taxpayers paid for a substantial part of the human genome project and deserve the benefits.

I had the pleasure of being part of the National Advisory Committee for Human Genome Research back in the 1990s, headed by Dr. Francis Collins, and there was a continual refrain, "This is for the public benefit. This is about improving Americans' healthcare."

So, again, I endorse your suggestion.

DR. GUTMANN: Great.

John?

DR. ARRAS: My previous comment is now redundant.

(Laughter.)

I agree with everything that has been said. I think we should also link this up with our synthetic biology report, where we do make a very similar recommendation.

DR. GUTMANN: Good, good.

Raju?

DR. KUCHERLAPATI: I am also supportive of this, but I also wanted to say that, in 2001, when the draft human genome sequence was completed, it was estimated that it would cost about $2.5 billion. The NIH put out an RFA to say that we would like to encourage technologies to sequence the human genome for $100,000.

DR. GUTMANN: Yes.

DR. KUCHERLAPATI: And several years later, they said that we would support research to make it $10,000, and so on.

And that investment that the federal government has put in has not only brought down the cost of this, but there is also a very significant amount of return on that investment, both in terms of investment from the private enterprise, as well as all the health benefits that we are talking about.

And so, I think that there may be an opportunity here within the context of this recommendation --

DR. GUTMANN: Yes.

DR. KUCHERLAPATI: -- to point out the great amount of benefit that was derived and to encourage the federal government to continue to support both the technology and research in this area.

DR. GUTMANN: Yes. No, I think that that is a very good prologue to the recommendation, the prescriptive part of the recommendation moving forward, because, as you know, also, we are entering an era that has been characterized as an era of personalized medicine. It is really important that not only people of means have access to that.

As discoveries are coming, there is the real possibility of providing broader access. But, as Steve points out, there has to be the databases to underwrite the validity of the science and medicine to deliver it to all populations in this country and then around the world. And it won't happen just automatically or it will happen more slowly than it should if we just leave it to its own devices.

So, I think, Raju, it is the perfect preface to our recommendation, is to remind people of how much the federal investment has actually paid off to date. And now, looking forward, we see vast potential, and we want to make sure that the potential is for everybody who can benefit, not only those who have the means privately to do so.

Good. I think, with very few exceptions, we are ready to move forward. We will caucus and just figure out whether we want to expand and delay or conclude and point to a future possible report. But, other than that and a lot more work in drafting the text, which we will review and will help staff, but we have had a great set of meetings.

I would just ask, is there anybody in the audience who would like to make a comment or ask a question? We do have five minutes and we have something here. Great.

Jim, why don't you read them because I have been talking a lot?

(Laughter.)

DR. WAGNER: I am happy to do it.

Actually, these are from Dr. Ed Gabriele again. I think, actually, Dr. Gabriele, his first one is about confusion regarding informed consent in the clinical healthcare versus research. I think Raju helped straighten out the Commission on the fact that these are entirely different levels of robustness that we need to keep into account there. So, that was a comment.

The second one, "OHRP is not in charge of human research nationally." Let me go to the ones I understand, and I may ask you to stand up on that one.

"What is the impact of what we are not doing on already-existing repositories?" That is a question we haven't talked about, and he gives as an example military tissue samples at what was formerly the AFIP. What do we imagine the impact of this is going to be on existing databases?

Nita?

DR. FARAHANY: So, a lot of the consent issues could have implications for existing databases, particularly if one of the things that emerged from this is a requirement to reconsent for new processes. But it will ultimately depend on how any sort of legislative response would be structured, because a legislative response could grandfather in existing samples or it could required that, if there are new approaches, that it would expand beyond and require reconsent.

Most likely, given that many of the samples are de-identified, except in the military context where they are maintained with specific regulations with respect to when they can be sampled generally to match a sample after there has been a loss, you know, in

those contexts, because most of them are going to be de-identified, I would assume that any kind of legislative response is going to consider that and not require reconsent or re-identification in order to access all those individuals.

So, that is an important thing to consider and I think a valuable thing for us to note in our report, that any legislative response should take into consideration existing databases.

DR. WAGNER: Do you think others agree with that?

DR. FARAHANY: Yes.

DR. WAGNER: Thanks, Nita.

His final comment is to make sure we are aware of a five-point donor process that is used by Navy Medical Research. I am not. Could you give us 15 seconds on what that is, sir?

DR. GABRIELE: Back a number of years ago, what we did was we instituted in the informed-consent process when there was a donor of samples that there were very specific questions that were asked. "Are you donating? Do you want it identified? If we do anything in the future, do you want to be notified?", et cetera, et cetera, and so forth, to make sure that those parameters were known as part, not only in the paper, but part of the dialog between the person doing the consensus --

DR. GUTMANN: So, Dr. Gabriele, would you forward to us something, a written summary of that process, because it would be great for us to cite it?

DR. GABRIELE: Sure. Happy to --

DR. GUTMANN: That would be terrific.

DR. GABRIELE: Yes, I would be happy to do that.

DR. WAGNER: Link us to it somehow, yes.

DR. GUTMANN: Great.

DR. WAGNER: Thank you very much.

DR. GUTMANN: So, we are going to take a 15-minute break. I want to thank all members of the Commission. We will reconvene at 11:00 a.m.