GENETICS SUBCOMMITTEE OF THE NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

DR. MURRAY: If the commission would all be seated, we would like to convene this meeting. Welcome to the meeting of the Genetics Subcommittee of the National Bioethics Advisory Commission.

Today's meeting will be devoted principally to a discussion of the Report on Tissue Samples.

Tomorrow there will be a meeting of the full commission, and the day after, the morning after that will be a meeting of the Human Subjects Subcommittee.

I have been asked to remind all the members of the commission to please, please pull your microphones forward when you have something to say. You can leave them there. That is fine.

I wonder if Dr. Harold Shapiro would have anything he would like to say in welcome?

DR. SHAPIRO: I simply would like to welcome all members of the commission and once again, for those of you I may not have said so directly, happy New Year to everyone. I look forward to working with you during this year.

I will make a somewhat more formal announcement tomorrow morning, but I do want to indicate that Dr. Eric Meslin has been appointed executive director

of the commission and so we are all very pleased. Eric, why don't you stand?

(Applause.)

DR. SHAPIRO: I know Bill Raub will be only too happy to go back to his regular full-time job. I will take this moment also to thank him, although he is not here, for his work on our behalf during a good part of last year.

So I will ask the staff to make sure that we all have coffee prepared by tomorrow morning. And I will have more to say at that time.

But, Eric, welcome. It is great to have you with us. I look forward to our discussions.

DR. MURRAY: Good. Let me join you in welcoming Eric aboard. It is good to have you here, Eric. My regrets to the ELSI Program, but tough.

DR. SHAPIRO: That is the spirit.

(Laughter.)

DR. MURRAY: Well, they would have done it to us if they could have.

DR. SHAPIRO: Right.

DR. MURRAY: No question. Let us get to--

DR. SHAPIRO: They did do it.

(Laughter.)

DR. MURRAY: That is true. That is right. They have been recruiting in our midst, haven't they, so it is only fair.

DISCUSSION OF TISSUE SAMPLES REPORT

KATHI E. HANNA, Ph.D., AND

SUBCOMMITTEE MEMBERS

DR. MURRAY: We are going to talk about the Tissue Sample Report, and we have-- Commissioners should have a draft of sections of the report. They should have had it for a week or two now. No? One week or so now.

Kathi Hanna has been working hard on it, including over the holidays, and I want to thank Kathi on behalf of all of us for what you have done. But we should jump into the report.

Now, Kathi, we want to go over each of the sections, I think, both the ones of which we have a draft, and the ones that we just have still an outline. I am going to ask Kathi in a moment if she has any specific needs that she would like us to address.

I have two things I want to mention. The first is I have a series of specific questions that I think we probably haven't talked enough about, even as a subcommittee, to know precisely what we want to say in the report, and I want us to get to them. You may have other

candidates.

The second thing is, and I will try to resist the temptation myself even as I remind my fellow commissioners to resist it, this is not the time for copy editing. If you have large comments about organizational scope, yes; about sections that need to be in there, yes; but this is not the time to correct spelling or the precise words. Write it down, give it to Kathi, and she and I will make sure it is taken care of.

Is everyone in agreement with that? Now, the temptation is very great because that is something we can fix on and do, but it is-- I think we are better off using our time to talk about the larger issues.

Kathi, what would you like to see us do?

DR. HANNA: Well, I think it is pretty obvious which sections need to be discussed. I think that the overview is obviously just my first attempt to try and forecast what issues are going to be covered in the report, so anything that is missing from that section I would appreciate your input on.

I think that the second chapter, which is really just a slightly condensed version of Elisa Eisman's report, there I think you just need to make decisions about how comprehensive you want to be. I think it is

still too long, but I left a lot of the examples in there so that there was at least information for people who were looking at this for the first time.

For the third chapter, the moral and religious perspectives, I think we have a lot of information to work with from Courtney Campbell.

We still are waiting to hear whether we have someone lined up to write a commissioned paper on some of the other issues that are not necessarily, that don't necessarily have a religious orientation.

So that really leaves-- I think where we need to do the most work in is Chapters IV and actually VI, since Chapter V will be mostly descriptive and that is going to be fairly straightforward.

Other than that I think I just, you know, this is very patchy draft at this point and I think we need to focus. I can work from the transcripts and previous discussions on Chapter IV, but I think Chapter VI, where you really have to operationalize your recommendations, is where we need to do the most work.

DR. MURRAY: Okay. Trish?

MS. BACKLAR: I just would like to say that, in Chapter I, that we shouldn't forget that we really need to look in some way at the issue of minimal risk as we are

also looking at the Human Subjects Subcommittee. And you may not want to do that now because--

(Technical difficulties.)

DR. MURRAY: I know that has come up in some of the discussions about tissue samples, including the National Action Plan and previous discussions.

MS. BACKLAR: And we are--many of us--really considering the detail--

(Technical difficulties.)

DR. MURRAY: Yes.

MS. BACKLAR: So we might share some of that together.

DR. MURRAY: Yes. Yes. Yes.

DR. GREIDER: I have a couple of comments, and the first is on the outline. And I apologize that I wasn't there for all of the discussion when we discussed the orders and what the actual tactics were going to be.

But it seemed to me, looking over this proposed outline, that the public knowledge and beliefs is relegated to an appendix rather than a chapter, and I am just wondering if we would consider actually having that be part and parcel of the whole thing rather than putting that in an appendix at the back.

And I am not sure what kind of discussion

occurred since I wasn't here at the end of the meeting when we discussed the outline why it is an appendix.

And my recommendation would be to have it be a chapter following the science Chapter II. So something along the lines of, you know, what are the public views on this, earlier rather than as an appendix.

DR. MURRAY: This is the time to talk about the overall organization of the report. I think that is a good way to jump in. We had a discussion about that organization at the end of the last meeting, but that was not having a draft in front of us and, you know, your ideas get more concrete the more you have to look at.

Larry?

DR. MIIKE: A couple of comments. The framework Chapter IV, if we are going to be discussing the issues around which we then reach our conclusions in Chapter VI, then that is okay, but the way I, the way I glanced at Chapter IV, it seemed to mix both.

So you are either going to have to combine IV and VI and make it follow V, or you are going to have to have a discussion of the framework and then the policy recommendations coming later.

But in either event, I think just in sequential things, the currently-proposed policy should

come before our framework because that sort of bores out there right now, and then we impose our own framework on top of that.

The other problem is that I don't what to do with the religious chapter because I don't see the moral piece. And if I don't see the moral piece I don't know how useful the religious chapter is going to be in balancing that off.

If we keep the religious chapter there, then I would take out the conclusion section and more or less say that the religious discussion leads to the same kinds of conclusions that we reach in the--for lack of a better word--the lay approach that the rest of us think, which is that it gives the same kinds of conclusions that we would have reached regardless of a religious perspective.

Do you understand? When somebody talks about confidentiality, community, et cetera, et cetera, and those are not things that necessarily-- Particularly from the religious standpoint, I think it is something that we have all discussed.

So I think that perhaps that we should say that, even when you come from this religious perspective, we sort of arrive at the same point, regardless of whether we are coming from a religious perspective, or from a

scientific perspective, or a social perspective, or whatever.

DR. MURRAY: Kathi, you had something to say before. Did you want to say it now?

DR. HANNA: Yes. I just wanted to respond to Carol's comment about moving the section on public knowledge to an appendix.

I think we are still not quite sure what to do with that section, and part of it is because I think there is some discomfort about the reliability and the validity of the mini-hearings' approach as a good gauge, other than just one indicator.

And so I think what Eric and I have talked about doing is trying to find some other opinion polls, surveys, systematic types of measures, that can then be viewed as complementary to the piece that is being done, the mini-hearings. So I think the--

The other thing is that there are some interesting things that have come out of the mini-hearings that I think we should try and incorporate throughout the report as they arise, and not just segregate public opinion to its own section, but really try and, if it is relevant, refer to it in the chapter where it is appropriate.

DR. MURRAY: Bette?

MS. KRAMER: Excuse me. I understand the concern about the--

(Technical difficulties.)

MS. KRAMER: --and I know it is important to put it into the body of the report as opposed to an appendix because if you think back to our concerns that led to the mini-hearings it was the fact that, even though all of the--

(Technical difficulties.)

MS. KRAMER: So I think that if you put it in the context of recognizing that this is not a full-blown scientific poll, such as--

(Technical difficulties.)

MS. KRAMER: --but put in a context of our attempt to get some feedback from the public. And then I don't know legally--

(Technical difficulties.)

MS. KRAMER: And I hate to see it regulated to an appendix because I think it indicates a lack of concern of the public--

(Technical difficulties.)

DR. MURRAY: Carol?

DR. GREIDER: I agree with you, Bette. That

was sort of why I initially brought this up.

I also wanted to respond to Kathi that I think it is also true to incorporate as much of it as we can into other chapters. I very much agree with that.

I was just responding to the fact that it seemed to me to be a relatively important thing to many of the commissioners that we get this information rather than sort of operating in a vacuum, and I didn't want that issue to be an afterthought the way the report came out.

DR. MURRAY: Zeke?

DR. EMANUEL: Two things.

(Technical difficulties.)

DR. EMANUEL: --and I suggested, one of the reasons I asked Janet Wells(?) to come up with those questions was really incorporate it--

(Technical difficulties.)

DR. EMANUEL: --sometime in the next few months, but not--

(Technical difficulties.)

DR. EMANUEL: Having those questions and maybe even including them during--

(Technical difficulties.)

DR. EMANUEL: My own suggestion is that we still have a lot of boxology--

(Technical difficulties.)

DR. EMANUEL: And my only suggestion is that, once we resolve that, at least we can more or less decide what the framework is. And at least on eye level there was some disagreement and uncertainty about the boxes, and I apologize for the boxes.

(Technical difficulties.)

DR. EMANUEL: But we had talked about whether, on previous samples, we were going to combine research and clinical care and we had talked about how we--

(Technical difficulties.)

DR. EMANUEL: I mean, I think that those are the most important issues for us--

(Technical difficulties.)

DR. MURRAY: Yes. I think, particularly with Zeke here, we ought to take what time we have with him to try to look at the boxes, but I want to recognize Bernie and David.

DR. LO: David and I are--

(Technical difficulties.)

DR. LO: --little bit while I was swimming this morning, so this may be all wet.

(Laughter.)

(Technical difficulties.)

DR. LO: But it struck us, as we sort of stepped back from where we are around the-- We were concerned we may have lost sight of--

(Technical difficulties.)

DR. LO: I didn't really have a clear picture until I spoke with David about--

(Technical difficulties.)

DR. LO: One has to do with, as I said, just sort of what makes genetics DNA research--

(Technical difficulties.)

DR. LO: And, on the one hand, I think I would ask that we stress this firewall that we started to talk about and the way that we address--

(Technical difficulties.)

DR. LO: One direction is, as the researcher discovers things that are going to have potential clinical significance--

(Technical difficulties.)

DR. LO: So I think as long as we have a possibility of--

(Technical difficulties.)

DR. LO: So I think how we handle that is important when we are thinking about it.

I think it also may fall under pressure in the

opposite direction, and this I--

(Technical difficulties.)

DR. LO: And David came up with a model of using a large--

(Technical difficulties.)

DR. LO: The problem I see come up, when I signed up for that study, I said, you can only use my tissue for the disease of interest and--

(Technical difficulties.)

DR. LO: And one of the things I would like to see is this notion that along--

(Technical difficulties.)

DR. LO: I think we should sort of try to think about all those and anticipate those sorts of problems.

(Technical difficulties.)

DR. COX: Yes. Well, I run a risk of saying anything--

DR. MURRAY: David, would you bring your microphone closer? Thank you.

DR. COX: Because in the past, when I have tried to articulate these things, I have been totally incomprehensible, so I will try yet one more time, but if I am incomprehensible yet again, please tell me.

The-- Bernie has helped me with some of the words and the concepts and I guess one of them has to do with that there is several different processes of doing research, different study designs, and to focus on what that study design is--cross-cutting what the boxes are--gives a more whole picture to me.

And so it really has to do with not sort of what most of the samples are that are in existence now, but what are going to be the use of the samples in the future?

It is an important issue to deal with the retrospective studies--don't get me wrong--but I think that, in large part, our job as a commission is to think of where we stand now but, more importantly, where we are going in the future.

So in the second chapter, which I guess is the science chapter, because Carol and I are involved with that, and I think it is good to document what samples are there, but then, just like happened in cloning report, go through what the scientific process is, what some of the study design would be that could lay out what the structure for the future is going to be.

That is not sort of what the ethical boxology is, but it is saying practically how the research is going

to be carried out. Then that makes for a more whole discussion of--

It really boils down, in my mind, to this relationship of the subjects to the researchers, and that relationship is different in different settings, depending on how you do the design.

My personal belief is that, in genetics, the relationship between the researchers and the subjects is like tight. It always will be. All right? And that is very different from what is going on in epidemiology in general. So why is it tight in genetics?

And it is tight because of this stratification; taking big groups of people and winnowing them down to a narrower stratified subset of which you collect more and more information. And how you can have that kind of a process, where you divorce--in the long run, to come up with a treatment--where you divorce the researcher from the patient, I don't understand.

So my specific suggestion is, is that Carol and I--and others who want to--but in specifics, Carol and I work on the second chapter to include that kind of a process of the kinds of research that may be going on, different types of research, and what is involved with that in terms of these relationships, because I think it

complements the structure of the boxology.

And then--I quite agree with what Larry said--that then putting those two together we come up with the recommendations on it.

DR. EMANUEL: I am a little confused. I need some context--

(Technical difficulties.)

DR. EMANUEL: And I think this is a situation where we are talking about it. You want to go back to the Physician's Health Study or to the Framingham Health Study and do genetics on samples that were not initially collected for genetic tests.

(Technical difficulties.)

DR. EMANUEL: There is no relationship between the researcher there and the--

(Technical difficulties.)

DR. EMANUEL: No relationship. Even if you did accomplish--

(Technical difficulties.)

DR. COX: Okay. I understand, Zeke.

DR. EMANUEL: So the issue that Bernie suggested, you know, now once--

(Technical difficulties.)

DR. EMANUEL: You don't know who these 10,000

are. They are just numbers.

DR. COX: That is correct. So let us back up for a second and say, ultimately, what is the goal of genetics research?

It is not to find a gene that predicts something. This is my personal view. It is not to find a gene that can predict that you are going to die when you are, you know, 43. Okay? It is to come up with treatments to improve people's health.

So that what is the process by which, in my view of the future, that this is going to happen? It is going to start with very large populations like the Framingham or NHANES.

The initial part of it is going to be finding associations of genes that do make predictions. All right? Not all DNA information is going to be highly predictive, but a subset of it will be very predictive.

But that is just the beginning because, when you get those predictions, then you have individuals who you can make predictions about but there is no therapies or any options.

How then is science going to proceed to come up with any therapies or options? It is going to be to enlist exactly that subset of people to do clinical trials

to figure out what works and what doesn't work. That is where the relationship comes in.

DR. EMANUEL: (Inaudible.)

DR. COX: So it is not stopping when you find the association.

(Simultaneous discussion.)

DR. EMANUEL: Right. It is also a completely different type of research protocol that is separate from going back to the stored tissues. Right? I mean, that is--

(Technical difficulties.)

DR. EMANUEL: Right? I agree with you. Then what you do is you go back, find the people who got that genetic alteration and--

(Technical difficulties.)

DR. COX: But see, now we are going to-- Follow me one more step now. So now we are with those individuals and that one set of researchers is getting more and more information about then and are involved with clinical trials.

Now, another group of researchers, because these happen to be heart doctors because they are working on ApoE, but now another group of researchers says, "Guess what? Your ApoE is important for Alzheimer's disease, not

just heart disease, and so we want to enlist you in this." All right?

So that what it means is that if, when patients get involved with us to begin with, they are part of an overall process that they may or may not want to be part of, but you can't inform them about it from the very get-go, so--

(Technical difficulties.)

DR. EMANUEL: --this kind of example because the question is, is it covered in a way we feel comfortable with or is it not covered in a way that you--

(Technical difficulties.)

DR. MURRAY: Yes.

DR. EMANUEL: Is that what we are here for?

DR. MURRAY: Yes. You are here until 2:30 p.m.?

DR. EMANUEL: Yes.

DR. MURRAY: Okay.

DR. EMANUEL: I apologize.

DR. MURRAY: Well, I think we should use you while you are here as extensively as we can, so why don't you do that?

DR. EMANUEL: So let us say we have a stored sample, like the Framingham Health Study, so it is a

previously collected sample. Right? And we are not going to--

(Technical difficulties.)

DR. EMANUEL: Right? So I am not sure why that isn't on the boxology 1a. Is that 1a?

DR. COX: Well, you tell me.

(Technical difficulties.)

DR. EMANUEL: Okay? Now say you have found that and in your first study, you know, you notice, in the Framingham, it is associated with the Ashkenazi Jewish population, and you go to another Ashkenazi Jewish cohort that has--

(Technical difficulties.)

DR. COX: I don't want to go to a different cohort though Zeke. I want to take the people that I have begun to find in Framingham because there is not so many of them there, and it costs me a lot of money to find them, and I want to do more stuff with them.

DR. EMANUEL: Okay. So I think the issue is what does "more stuff" mean?

DR. COX: More stuff means collecting--

(Technical difficulties.)

DR. EMANUEL: Collecting more clinical information, if it is done in an anonymous manner with the

firewall, is perfectly fine--as I understood our agreement last time--is perfectly fine in box 1a. We want continuous information--b--as long as it is in an anonymous manner, and you can't identify that particular person.

Now--

DR. MURRAY: Instrumentally, as I understand it, to see if I am following, what this would entail would be the researcher, you, now wanting additional information and more samples, going back to the stewart of the samples.

DR. EMANUEL: And who is the stewart of the sample?

DR. MURRAY: Presumably it might be a pathology department.

And saying, you know, these were very fruitful samples. I would appreciate additional sample material and additional clinical information, but it can also be-- It could still remain anonymous. Is this what you are contemplating?

DR. COX: Well--

DR. EMANUEL: But imagine two different circumstances. Imagine you have a research study, again like the Physician's Health Study or NHANES. You are--

That data is being dumped into this anonymous pool. That is the way you have created the situation. So you have got the data up until that point.

Say two years later they do another survey of these people--right?--to find out, you know, what diseases have happened in the intervening two years, the way they do in the Physician's Health Study. That data, as it is entered, gets dumped in and there is an update.

DR. COX: Yes. But what if it is not the data that I want, Zeke?

DR. EMANUEL: What if it is--

DR. COX: Not the information that I want.

DR. EMANUEL: So you-- So now the question is, you want to walk backwards, identify those particular 12 people--

DR. COX: This is how genetics is done. So that you go and you stratify populations and you intensively investigate a smaller subset.

DR. EMANUEL: I think if you then want to be able to use it in an identifiable manner, you are going to have to get their consent. I mean, that is what this says. Then you move to 1b. And then you would have to get their consent.

DR. LO: Okay. But that is-- I think that is

important that you can't sort of say the trustee goes back to the patient and negotiates and then anonymizes it so that, when I get it as a researcher, it is anonymous.

DR. EMANUEL: Well, I think we are going-- I think we are-- I think by not having a good example, we are sloshing a little back and forth.

In my mind--and I am only one member here--the trustee situation is a-- That operates really in the clinical where you have got the sample from the clinical context.

Remember, in the Physician's Health Study, you have got freezers full, you have got it computerized, you have got a database. All right? There you have got an organization already.

In the sort of clinical setting where you have gone and you want, you know, like the Angiogenesis Factor Study from the Brigham, you want samples of breast cancer with, you know, five to 10 years of follow up, and they are the trustee who pulls them out, who knows which ones they have pulled, and has gone to the clinical record and added that information to you. That-- There is a trustee.

In a research setting, there is not a single person like that pathologist. Right? I mean, there is a

whole infrastructure to dealing with 30,000 or 60,000 people. And that is a completely different setting I think.

DR. LO: Right. I think the point I would want to try to make is that we need to think through what are the characteristics of either the trustee or the decision-making entity within the larger study that are such that we would feel comfortable saying they can make these decisions and, in particular, whether there should be some input in these research studies from the community as to when you cross the line from 1a to 1b because I think there are going to be a lot of judgement calls.

And I think that, in the way this is interpreted in practice, I wouldn't want people to not be aware of the nuances and the controversies.

DR. MURRAY: Carol had something to say.

DR. GREIDER: I am going to agree with a lot of what you were saying, Zeke.

And I think that one of the things that would help us all out is just to define specifically how we are going to deal with each of the situations, what the scenarios are in box 1a and 1b and 1c and 1d, and what kinds of protocols we would like to see put in place for each one of those different cases.

I mean, I think you are all bringing up specific cases, and I think that they all are covered by this framework. We just have to be very specific about how we define what goes into what box.

If we are having trouble here, that doesn't bode well for other groups in the future. So if we can be more specific and lay out the details. And I agree with you; we have got to do the boxology to do that.

DR. MURRAY: Bette?

MS. KRAMER: I am wondering if we don't have to go back further; thinking about what Bernie said about people who have opted out who might, for the benefit of further knowledge, have changed their mind.

And if I recall correctly in the mini-hearings, just about every group, there were a preponderance of the members, the people there, who said that they would want to find out. At least that is my memory from the presentations and looking it over.

So I wonder if what we really need to take a look at is the opt-out process?

DR. GREIDER: But that fits within one of the boxes, right? That is one of the--

MS. KRAMER: Yes. Right. But it is--

DR. GREIDER: --criteria.

MS. KRAMER: It is more procedural than--

DR. GREIDER: It is filling in with what you are going to do in the specific instances; it is not changing the framework. I mean, I think it would be--

MS. KRAMER: So that doesn't change the framework.

DR. EMANUEL: I think again, Bette, we have to distinguish. If you are using a sample in an anonymous manner, you don't know. I mean, what that means is you can't link result A with person B. That is what it means. Okay? So you can't actually go back to that.

If you are using it in a potentially identifiable manner, which would make it 1b, or any of the b's, you can go back to them, but that would have required consent in the first place.

Now, I think we need to-- I am comfortable with that and I would-- You know, we can argue about that, and we did argue about it in the previous-- But I think that does cover the cases and how you can go back.

If it is truly in an anonymous manner. I mean, if that is what that firewall is about, you can't walk backwards. We get that information. We can't link A to B. I mean, that--

DR. MURRAY: Harold and Larry have been

waiting.

DR. SHAPIRO: Thank you. I want to ask a series of questions just to test my own understanding of this because I haven't been part of all of these hearings and I just want to make sure that I understand what is laid out here. And I will try to do it within the context of these boxes.

I understand what is meant by use in an anonymous manner to have nothing to do with how it is collected, but it has to do with the nature of the researcher's--in this case--knowledge or capacity to go back to the original sources. In an anonymous manner means there is some kind of wall there so that a researcher cannot go back. Is that-- That is correct?

DR. EMANUEL: Right. We think that is one of our breakthroughs.

DR. SHAPIRO: Okay. No. I just want to understand. That is what I thought and I have no objection to that.

And I think Bernie's point is that that wall is going to achieve a certain kind of dynamic over time and we may want to address that. I understand that we will come back to that a little bit after.

I take it that it is true, in all these boxes,

that an opt out is always possible; there is no reason why anyone should-- Right? You have opt out in some cases and not in other cases?

DR. EMANUEL: No. That is not true.

DR. SHAPIRO: Okay.

DR. EMANUEL: You have to distinguish previously collected samples.

DR. SHAPIRO: Yes.

DR. EMANUEL: The 238 million existent samples--

DR. SHAPIRO: Right.

DR. EMANUEL: --from the prospectively collected samples.

DR. SHAPIRO: Yes.

DR. EMANUEL: Okay? In the previously collected samples, when you went in for your breast biopsy, no, they didn't ask you about anything, right? You actually probably signed away your rights in a way that you had no idea.

DR. SHAPIRO: Right.

DR. EMANUEL: In the prospectively collected sample, we want to make that an explicit part of the process.

DR. SHAPIRO: Okay. So the answer is that opt

out-- The privilege of opting out of a study, should you know about it, depends on where you fall in one of these boxes?

DR. EMANUEL: No. I wouldn't have put it that way. The privilege of opting out of any study is reserved for two categories. One is if your sample is going to be used in an identifiable manner, and, in general way, in prospectively collected samples.

DR. SHAPIRO: Okay. So it is only the right-hand side?

DR. EMANUEL: Well, and also all the b's.

DR. SHAPIRO: Along with some columns.

(Simultaneous discussion.)

DR. EMANUEL: All the b's. 1b, 2b and 3b.

DR. SHAPIRO: Okay. I will come back to that later.

Again, just for clarification, I don't know if we are all looking at the same table here, since there is quite a number of them at the end, but the one that is most fully filled out is the one that I am looking at.

If I look at 2a and 3a, or 2c and 3c, or 2e and 3e, or the bottom two squares in the anonymous manner, in each case, is it the case that they should read exactly the same as 1a, c and e?

Because I can't understand why 2a, 3a, et cetera--the bottom part of those columns where they are in an individually anonymous manner--should be any different from the bottom two squares and the top square.

What have I lost here?

DR. LO: Well, we do--

DR. GREIDER: I don't think we are looking at the correct version of filling in.

DR. EMANUEL: Right. Right.

DR. GREIDER: Right. What I have is the filled in thing and what I think Zeke mentioned is that this was a number we agreed on and--

DR. EMANUEL: Right. I have revised that.

DR. SHAPIRO: I am just asking a question. I am not challenging anything. I am just asking whether square 2a and 3a, properly filled in, are any different than 1a?

DR. EMANUEL: Yes.

DR. SHAPIRO: Okay. Well, that I don't-- I don't want to take up time now, since I don't understand that, so one of the members will explain that to me later. I am just--

DR. EMANUEL: Actually, that is-- No. But that is the heart of part of this boxology. Okay.

DR. SHAPIRO: Well, okay.

DR. EMANUEL: And now I think I understand. The question is why isn't everything just 1?

DR. SHAPIRO: Not everything. No. I am just talking about a. Let us take column a.

DR. EMANUEL: Oh.

DR. SHAPIRO: Column a.

DR. LO: It is the community.

DR. EMANUEL: It is the community issue.

DR. SHAPIRO: But it is anonymous, so who knows anything about community?

DR. EMANUEL: Because sometimes you go to particular samples that identify a community.

For example, a colon cancer gene where you were trying to identify Ashkenazi Jews, you just didn't go to any sample, you went to a particular sample that you could associate with--

DR. SHAPIRO: So anonymous in this case is only partly anonymous; that is, you can't identify the individual.

DR. MIIKE: That is what we mean by--

DR. EMANUEL: By anonymous.

DR. MURRAY: You can't identify the--

DR. SHAPIRO: All right. I didn't understand

that. Okay.

DR. MURRAY: But it may well-- I mean, very little of these tissue samples are useful without some demographic information or illness history.

DR. EMANUEL: If you actually look at the very last table--this is I think not updated since our last meeting, but updated from our previous meeting--it now says to be used in an individually anonymous manner and the word--

Maybe we should have stressed or highlighted or bolded "individually" there, because what it means is that you can't identify an individual, but you might be able, through demographics, like Tom says, identify from which community they might come. You might have gone to a particular community to get the sample.

DR. SHAPIRO: Okay. So it just means I don't know their name; I may know something about their--

DR. EMANUEL: A lot about them.

DR. SHAPIRO: --religion, or about their race, or about something else?

DR. EMANUEL: Right.

DR. MURRAY: Yes, as an individual. Right.

DR. EMANUEL: To emphasize, again the current regs, the common rule only recognizes that box, 1a. It

doesn't recognize--

DR. SHAPIRO: Well, I assume--

DR. EMANUEL: --the other boxes.

DR. SHAPIRO: Yes. Okay.

DR. MURRAY: Larry?

DR. MIIKE: Yes. I want to get back to what Dave was having a discussion with Zeke about, which was he wants more information and so he wants to get back to the individuals who provided the original sample.

The variable in here is this trustee concept because it seems to me that that is an issue we have got to address. When is there a trustee who acts in place and just sort of a shepherd of the existing information, and when does the individual have to be brought in?

At a simplified level, one could say the trustee is there for information that is already in a record somewhere and does not need to be continually collected off an individual.

If information is being continually collected off an individual, that person is actively involved and should be--should be--sought after and said do you want to participate in these future research topics?

So it seems to me that the question that if you want more information and you are concerned that your

model doesn't--your particular instance--doesn't fit in here, it depends on what is the relationship between the test subject and the researcher or the clinician.

DR. EMANUEL: Bingo. And that is exactly what--

DR. MIIKE: But it would still fit in these because that would be--

DR. EMANUEL: I thought you articulated it right.

DR. MIIKE: Yes. Because it would fit in one of your boxes.

DR. EMANUEL: If you are getting information from an existing pool--

DR. MIIKE: Right.

DR. EMANUEL: Right? Existant data that you are going to use in an anonymous manner, then it is in the to be used in an anonymous manner.

If you need to go back to the subject and get additional information from that subject-- Right? You have got-- You are using it in an identifiable manner and you are wishing to collect special information that isn't extant.

First of all, that-- You know, 45 CFR 46 doesn't apply to that. I mean, that is new information

you are collecting as part of a research protocol. That is a new protocol and that means you need to get their consent.

DR. COX: No. Zeke, listen. It can fit into the boxes.

What my difficulty is, is that do the boxes-- What we, as NBAC, want to do with layout, you know, what the discussion, what the issues are--

And if what we do is we say--okay--that, because of privacy issues and because of the difficulties of doing research that, what we are going to do is say the paradigm by how the stuff should be done is that there is a firewall between the people doing research and the patients, I have a problem with that.

And the reason I have a problem with it is I think that the majority of the future research is going to require closer relationship, ongoing relationship, between the researchers and the patients because most of it is going to require more and more information and it is going to require continued consent.

The trustees are going to be the community-- not the individual patients--that you work with and that the researcher is very close with.

And so that my concern is not whether things

can fit in the boxes or not, but whether we are sending the message that isn't sort of consistent with reality.

DR. MIIKE: But you are not suggesting--

DR. EMANUEL: I don't see a--

DR. MIIKE: --that, in a continual relationship between a researcher and a subject, that once a subject gives consent he can't back out?

DR. COX: Absolutely not. I am not suggesting that at all. But I am saying that there--

I think that the vast majority of genetic research, at least at the level where it is going to count--not at the level of finding associations--is going to require a very close relationship between the researchers and the individuals in the communities involved.

DR. MIIKE: Okay. But can I just--

DR. COX: Yes.

DR. MIIKE: Then I think that we are in a different scenario. We are not talking about a piece of tissue lying there; we are talking about the real patient now. The tissue was the entry into that patient.

DR. COX: Correct.

DR. MIIKE: But you are into a different relationship.

DR. COX: Correct.

DR. EMANUEL: And that is a different kind of research effort. That is not stored tissue research which-- So I think we are-- I don't think we are in disagreement at all. I think-- I mean, that would require a regular, every-day old protocol that you can-- You already have to do now. It would require the patient's consent because they would be giving you additional information.

So I don't think it is-- I don't think it is the issue that we were addressing or, if it is the issue we are addressing, it requires informed consent.

And I now apologize for running out unfortunately at a very important discussion.

DR. COX: I agree with what you just said, Zeke, but I think that I would hope this is an issue that is on the table with respect to this because it is certainly broader than just dealing with the tissues that are sitting in somebody's freezer.

But when we are talking about the use of genetic information in stored tissues, I think that a lot of the action is in these broader issues and not just in what is in the freezer. That is my point.

DR. MURRAY: Thank you, Zeke. Sorry that you

have to leave, but I understand. We will see you tomorrow.

DR. EMANUEL: Yes.

DR. MURRAY: I had the bad form to cut Harold Shapiro off in mid-question, so let me give him a chance to finish.

DR. SHAPIRO: Well, let me-- Someone tell me if I am not speaking articulately into this microphone.

As I look at this table, which does seem to cover most of the cases I can think through one way or the other, although the problem of the wall remains and its dynamic nature, would it be true that if you look at the segment of the matrix that deals with existing samples, that is the left two columns, if I understand this correctly, that the nature of the original consent might somehow matter?

And I don't have any suggestion to make. I just have an observation that we deal with those two columns. You may or may not have an original consent of some kind--I don't know the vast variety of things, I expect--and I am just suggesting that that might matter.

DR. GREIDER: I think that we discussed that the last time and that we were sort of going for the least common denominator approach, assuming that it was the

thinnest possible, if any, consent and giving protections to that--

DR. MURRAY: When we were--

DR. GREIDER: --scenario.

DR. MURRAY: Yes. Go ahead, Carol. I am sorry.

DR. GREIDER: That is all.

DR. MURRAY: When we were being careful in spelling some of this out, we made the point that if there was, with the consent for a tissue sample, some reasonable indication that it would not have been, the person would not have wanted it to be used for X, then it ought not to be used for X.

So if there is any indication with the sample that there was, you know, that someone checked the do not use my tissue for research, then you don't use it for research, or if there was some other question that was asked which would indicate someone wouldn't want their tissue to be used--

DR. SHAPIRO: Okay. So the assumption is, as we go ahead here, that is a minimal consent, whatever minimal is. Not being asked I guess is the minimal.

Okay. If I can make a few other comments. There is just related questions because I don't--

And that is the issue of community consent becomes very large in these new rows here, the second and third row of the matrix, and I certainly understand why.

The question I have, Tom, is whether the committee has given any consideration or talk about just what that would mean?

We tend to talk about it as community involvement, which I understand much better than community consent actually. And one suggestion I have, which came out of really a conversation I had with Eric this morning, is that that might actually be a better word to use. But I leave that--

DR. MURRAY: Which?

DR. SHAPIRO: Involvement.

DR. MURRAY: Well, where actually? I was disappointed to see it described as community consent here because I think we had moved to the notion of community consultation at our last meeting.

DR. SHAPIRO: Okay. All right. So that is just-- I am sorry it hadn't caught up with me.

DR. MURRAY: Okay. It wasn't in the document.

DR. SHAPIRO: Yes. Another question that I have is--let me also just put it as a question--in your own thinking about this, on distinguishing from those that

have potential harms, and those that don't; that is, distinguishing in the second row and the third row.

In your own discussions, how does that happen? Where does-- How do you decide whether to throw something in one box, the second row or the third row?

DR. MIIKE: I think we punted on that and decided we could not be the body that could tease that out to the degree that would be satisfactory. Isn't that right?

DR. MURRAY: Bette and Bernie.

MS. KRAMER: I am having a little problem because I don't recall that we ever came to a final determination as to how we felt about community involvement, period. We seemed-- The last two meetings, as best I can recall, ended with those issues in the process of discussion but no decisions having been made.

So if I remember correctly, on the basis of what--excuse me--what I remember, what is in these boxes is what Zeke had prepared for us around which to have a discussion, but we have never come to a final decision.

Now, please correct me if I am wrong.

DR. MURRAY: No. I think you are right, although I sensed--probably by mere projection--I sensed a growing consensus that some notion of community

consultation was sensible, even though we had to define it better, flesh it out, and defend it. But we still have some of that work to do.

But Harold, I think, just asked a different question, which is how will we know, either in terms of substantive principles or some procedural arrangements, when to say that there is potential harm or no potential harm to the community?

Bernie and Carol.

DR. LO: Yes. If I can try and generalize from the last couple of comments, I think again I am concerned not with the boxes, per se, but who decides what fits into which box and who does that interpretation?

And I think it is fine if you have Zeke on call to say, "Well, wait a minute, let me think this through and let me explain to you why it is really in the box here rather than the box there." But you can have zillions of IRBs and zillions of investigators doing this on their own and--

DR. SHAPIRO: How many zeros are there in zillions?

DR. LO: Yes.

But my concern is that, unless we give this some guidance on these issues, the grid itself won't be as

useful. I mean, it is like any other sort of federal regulation on research. It is how the individual IRB struggles with it, and I think they need help on that.

One of the considerations they should take into account, deciding whether it is this column or that column, and I think just the issues Harold was raising; who decides? And, again, I would push to say that it doesn't make-- I would urge that we have some community input into whether there are potential harms or not, not just researchers or trustees, or whatever, or steering committees deciding it.

DR. MURRAY: Carol?

DR. GREIDER: I mean, just to directly address that issue, my understanding from our conversations was that it is the IRBs. That which box to assign it to is subject to IRB-- The researcher first says, "I think it fits blah," and the IRB says, "Yes, we agree with you," or, "No we don't agree with you; it belongs in the other box."

And then there is a series of recommendations about what would be done if it were in one box or the other.

But to get back to the specific question that Harold asked, I don't think that we even agreed that there

was a difference between 2 and 3. We were in the middle of discussing that; whether you could even make a difference between 2 and 3, or whether we should have one column or row for all of the community issues. And we were in the process of discussing that at the end of the meeting.

And from my recollection, we never decided whether that should be a 2 and a 3, or simply a 2. So we couldn't have addressed how to decide which goes in it if we hadn't really come to that conclusion. And I certainly wasn't convinced whether it was 1 or 2.

DR. MURRAY: My recollection of our conversations and interim conclusions corresponds to the one that Carol just reported.

I want to mention that if we were to decide that the distinction between no potential for harm and potential for harm, if we were to decide that was an important distinction, one we wanted to keep in the proposal, we have got three things to do.

One was the procedural thing, which is namely let the investigator give the investigator's view. The IRB then makes a determination. So we did get that far.

We haven't provided anything by way of substantive guidance as to what we think counts as

significant harm, nor have we given examples.

Now, I think it won't be that hard to come up with some examples, and it wouldn't be dishonorable to stop there; to give procedure, to talk about some examples, and to give some very general guidance, if we wanted to have that. We don't--

I am actually-- I think you can sometimes do as much harm by trying to sort of precisely specify all contingencies--

MS. BACKLAR: Right.

DR. MURRAY: --which you will never do well--

MS. BACKLAR: I think so.

DR. MURRAY: --or perfectly, than you will by giving some fairly flexible and vigorous procedure and some general guidance.

And that is-- I confess that is my bias in these matters.

Bernie?

DR. LO: There is no-- There may be another option there, Tom, and that is not to try and specify all contingencies, but to lay out the considerations you ought to take into account and some of the problems that--

DR. MURRAY: Yes. That is what I meant by general guidance. Absolutely.

DR. SHAPIRO: Tom, can I just make a comment?

DR. MURRAY: Yes.

DR. SHAPIRO: If you considered pulling together rows 2 and 3, and maybe that is what some of you want to do, and you went from consent, as you have already done--that is just a mistake in the layout--to consultation, then, if you make that move, the distinction between 2 and 3 becomes much smaller.

Because if you put community consultation in both 2 and 3, then it is less and less telling, it seems to me, to make distinctions between 2 and 3, so maybe those things are not independent of each other, at least as I react.

DR. MURRAY: I think that is a good point.

David?

DR. COX: So I-- This is again for my understanding of how the boxes are being used.

So now I am over on the right-hand side of the research protocol where people get informed consent to do a specific study with respect to high blood pressure. All right? And their samples-- And they are informed about that. That is the reason for the research. It is just a standard, you know, informed consent.

Now is it the case then, when those samples

are collected, that if somebody wants to use that for behavioral genetics research, in an anonymous fashion, that the researchers have access to that material?

DR. GREIDER: How were they collected? To be used in an anonymous manner or to be used in an identified manner?

DR. COX: They were collected to be used in an identifying manner.

DR. SHAPIRO: You don't make distinctions like that. You just-- You don't distinguish when you collect it; you just distinguish only how they are used.

DR. COX: That is right.

DR. MURRAY: Right.

DR. COX: So they were used--

DR. SHAPIRO: It doesn't matter.

DR. COX: --in an informed consent in an identified way.

DR. MIIKE: But now you are asking to use that in a different research protocol?

DR. COX: That is correct.

DR. MIIKE: You would need--

DR. COX: In an anonymous fashion.

DR. MIIKE: Well, in the original consent, they would consent to the research as well as a general

consent for use in other research areas so, if it is not identifiable, they have given a general consent and you would be able to use it.

DR. COX: Well-- But that is why I want to know what the consent is. This is what-- Because this is the practical issue of where this stands right now. There is-- Patients are being collected under specified research protocols and other people want to use those samples for other stuff and they don't want to be bothered by going back and asking if it was okay.

DR. MURRAY: Right.

DR. COX: So I am looking at how that fits into our boxes.

DR. MURRAY: Carol?

DR. GREIDER: One thing is how it fits in the boxes and another thing is what we are going to recommend; the kinds of informed consent that one should get.

DR. COX: Exactly.

DR. GREIDER: Right? I mean where it fits in the boxes is very easy to answer.

DR. COX: Okay. So--

DR. GREIDER: And the IRB would review it because it is a new protocol and say it fits in this box.

DR. COX: Well, then tell me where--

DR. GREIDER: The question then--

DR. COX: --it fits, because I don't see where it fits in the box.

DR. GREIDER: It fits-- It would be f, 1 or 2 or 3f. Research studies to be used so identification is possible.

DR. MIIKE: Well, he is talking about-- He is talking about anonymous. It would fit--

We had a--

DR. COX: It would fit under one box, and it wants to be used in another box.

DR. MURRAY: That is fine because we are focusing on the use.

DR. MIIKE: Use.

DR. MURRAY: When you are focusing on the manner of how-- In terms of-- In that set of our recommendations, which will deal with tissue to be collected in the future, we will deal also with the circumstances under which it is collected in the consent.

DR. MIIKE: Remember-- Yes.

DR. MURRAY: But our primary interest here is also--our primary interest, not is also--is with use, and whether or not a tissue is regarded as anonymous is anonymous in use or not.

DR. COX: No. But that is what I understand because that takes the participant in the research out of the picture.

DR. MURRAY: Right.

DR. COX: It is the user in terms of defining how they want to use it that has the control, the researcher. The subject no longer is involved unless the informed consent is appeared informed consent.

DR. MURRAY: Right.

DR. COX: That is the only point I am bringing up because--

DR. MURRAY: And I think-- We will look at possible ways that have been suggested about getting that consent, including getting consent say only for a particular study or a particular line of research versus a general consent to research which could not, at this point, be contemplated, the details of which couldn't be contemplated.

That simply are-- Those simply are some of the choices that exist right now, and we may or may not choose to recommend that they be incorporated in the sorts of consents that we envision once this report is in effect.

DR. LO: Tom?

DR. MURRAY: Yes?

DR. LO: If I could add one other point to this discussion, it seems to me that it is important that we keep clear the distinction between research context and clinical context; that we are pretty much in agreement that, in a clinical context, it is hard to imagine how practically speaking you can get a very detailed or thick informed consent.

And the only thing-- If I am conducting a big prospective cohort study where I am going to follow people over time, I ought to have ample opportunity to explain, have them ask questions, re-explain, and get a much more detailed consent.

And I think the thing that is striking about David's example isn't which box it fits in; it is the--

If I am asked to sign a general consent form and I am not really told what sorts of things I might be signing up for and, in particular, I am not told that there are certain types of genetic research that some scientists may be very eager to do that others find very controversial or down-right objectionable, if I am not told that, what I check off may not be very informed.

And I think that in our discussions of the extreme right-hand columns, which I think is different

than the clinical context discussions, we need to take into account that there is research and there is research.

And I think if I am thinking that it is all going to be for diseases like diseases I have, or things like cancer or heart attack, but someone else is really thinking of--whatever--behavioral things, or other types of really, you know, socially controversial and stigmatizing conditions, that ought to be part of the consent discussion.

DR. MURRAY: Yes. Yes.

DR. MIIKE: Well, I don't agree. I don't agree because what do we have-- It is not as though this is the only time that someone is going to review the research.

If it is going to be used in a controversial research topic sometime in the future, that is going to be reviewed by an IRB or other mechanism to see whether that is legitimate research, and the issues around that will come up.

DR. LO: Absolutely. But that is a different issue as to whether I want my sample used in that research. The research may be perfectly okay to the IRB, but I may, as an individual, say, "I choose to opt out." But you didn't--

DR. MIIKE: True. But you didn't-- But you have that choice if you are going to be identified. If you are not going-- If you are going to be anonymous, I don't see how you can-- I just don't see how, when you are being recruited into the research now, you can ever get any kind of a notion about possible uses in the future.

So, I mean, that is what our whole scheme is about, is about trying to protect that person if you use it in an anonymous manner or if you use it in an identifiable manner.

I mean, you know, what we are trying to do is trying to find a balance between the two, and I don't think you can use the entry into the initial research topic as the be-all and end-all about everything that will go on in the future.

DR. LO: Right. But see we draw different conclusions about it. So that depending on how much value you put on--

DR. MURRAY: Bernie, I am getting--

DR. LO: What?

DR. MURRAY: --clues that you need to act like a rock star and stick this right in your face when you talk.

DR. LO: So starting from that--

DR. MURRAY: Thank you.

DR. LO: --observation, you can either-- I mean, you can go two different ways.

One says it is so important that we not hamstring scientists that we are going to allow research to be used--material to be used--in an anonymous way even though the patient didn't really have very much idea of what they were getting into as opposed to saying some types of DNA-based genetics research may be so controversial we are going to bend the other way and make it a little harder for scientists and favorable to more of those subjects, albeit perhaps few--

DR. MIIKE: But that is a decision to be made in the future--

DR. LO: --who object.

DR. MIIKE: You can't make it at the time that someone is being recruited into a research topic, into a research protocol that has nothing to do with any future.

DR. LO: Well, can you at least tell me--

DR. MIIKE: I mean, sure. I mean, you know, I-- I mean, I will sign a form that says, "Don't use my tissue for unethical research." I mean, what good is it? I mean, there has got to be-- That decision has to be

made sometime in the future.

DR. LO: Maybe-- But my point is maybe we shouldn't-- I mean, another way to say it is that maybe we shouldn't-- It is not all clear to me that you should say that we are going to allow that research to be done because we can't go back and get consent later.

I mean, maybe the scientist who wants to do very controversial topics is going to have to put a little more effort into recruiting their subject and selling it on the merits of the research subject, not because the sample happens to be there.

DR. MURRAY: Trish and Bette have indicated they would like to speak.

Trish?

MS. BACKLAR: What is interesting about this is, of course, that we do use advance directives; the things in the future that we really don't know exactly what is going to occur. So there is some history that we have of dealing with the future which is, of course, uncertain and often unanticipated.

DR. MIIKE: Well, that is a different question from what he has raised, Trish. I can say it now; "I don't want my tissue to be used in the future." It is a different question that he raises. It is-- I agree with

you there are advance directives.

MS. BACKLAR: Correct. But we also have some history of advance directives that don't just say no; they also say this is what I would agree to, this is what I wouldn't agree to.

The problem with this is it becomes exceedingly complex. And I absolutely agree with Tom and Bernie in trying to keep this as open as possible. I didn't mean to direct you into this. I just wanted the point that there was something there; that we have some history.

And we may find it useful to suggest it in some way; that it could be employed in this. Not to close it off though.

DR. MURRAY: Thank you. Bette?

MS. KRAMER: I am having trouble understanding Bernie's objection because, if it is going to be used in an identified fashion, then it requires a full informed consent.

So if it is going to subsequently be used for a research study that had not been anticipated at the time that the subject was initially enrolled, then there is, without going back to that person, there is no way to get that full informed consent, so I think you have to make

the assumption-- You have got to I guess have to make one or two assumptions. Either it can't be used at all, or it can be used in an anonymized fashion.

DR. LO: That is a very different assumption.

MS. BACKLAR: Right.

DR. MURRAY: Right.

MS. BACKLAR: And I would like to go back to-- I would like to go back to a discussion that we had, a very brief discussion--gosh, I don't know--two or three meetings ago and that was when we raised a question of it is hard--

Before this is all over, aren't we all going to be part of a group, a community, to which somebody might feel there is stigma attached, and isn't that just a part of-- Isn't that just a part of the risk that we all accept, I mean, or that we should all accept?

DR. MURRAY: I-- Yes. Let me see if I can press Bernie's point because I think I understand the point, but I may come to a different judgement about it. I am not sure. Let me see if I can just press it.

Is it possible, under the kind of thing we are proposing, someone's tissue gathered under one set of circumstances, to then become part of a tissue collection and to then have the use of that tissue requested, in use

in an anonymized manner so that my identity doesn't go forward but my tissue does, that it might be used in a way that I would, if I had known about it in advance, find offensive?

And I think the answer has to be yes, that remains a possibility.

Now, what are the alternatives?

One alternative is to go back and knock on everybody's door and ask them for consent again. For a variety of reasons, that is seen as incredibly inefficient. Also at times impossible for certain people who will be untraceable or dead or whatever else. And also, in some cases, it might do more harm than good because people don't want to be re-contacted about certain things. They may not want to be reminded of so and so.

I guess the issue is, yes, there is a judgement here. That could happen. Are there any safeguards against it? There are at least two kinds of safeguards.

Safeguard number one is the IRB. And frankly if I were sitting on an IRB with such a proposal, to do something which I thought was explosive, my inclination would be to say to the investigator, "Look, I could easily see many people objecting to this so you better go out and

get some new samples from people who are consenting specifically to this study." That is protection number one.

Protection number two is if it implicates a particular group and it, you know, we keep that category in our proposal, then we have to get community consultation. And if the community says, "Hold on a minute; this is outrageous," then presumably the IRB is going to listen to that and say, "You can't go forward in the way you planned."

So there are levels of protection, number one. One and two, really.

DR. LO: No. I agree with what you and Larry both said about the IRB. My concern is are IRBs, as currently constituted, really fitted to play that role?

And I think having community consultation is important, but I think we have all seen a lot of examples of IRBs composed predominantly of members with affiliate, institutional affiliations just overlooking things that more public and community input might have pointed out.

DR. MURRAY: Right.

DR. COX: So that, Tom, that you just gave, was a very clear answer to the scenario that I laid out, which is if somebody comes in for a specified research

protocol to work on heart disease and somebody wants to do behavioral research anonymized, the answer is they can do it--okay?--with different projections.

DR. MURRAY: Well, that you can make the request to use it. Absolutely.

DR. COX: Now--

DR. MURRAY: You may not be granted the--

DR. COX: But it is anonymous. But now let us go one step further.

And the one step further is that there is a really fascinating result in that behavioral research and people really want to go back and they want to look at these people. The researchers want to do it. But they can't because there is a firewall. "Oh, well, I guess I just won't go back and look at it."

Give me a break. They are going to find out who these people are. I guarantee you they will. That is how it works. Okay. And those people are going to be contacted. I guarantee you they will. Now, that is how it works in the real world.

DR. MURRAY: Will you give us a guarantee in writing on that, David?

(Laughter.)

DR. COX: Yes. So-- Because I know my

colleagues that do this work. Okay? They are like bulldogs with respect to if they have an interesting scientific finding, nothing will get in their way.

So it is not that they are going to violate the law, but they will go and they will identify the physicians who worked with those people. Is it so hard to find these individuals? No.

So I am just saying that the firewall-- Okay? You can do encryption, you can do any kind of coding that you want so that the researcher doesn't have access, but so long as there are ties, there are ways for that to happen under the table.

Now, I quite appreciate what you are saying, which is to have to go back and talk to the patients every time when you do different types of research, that is not practical.

All I am doing is talking about the other side of it which is that, when the patients are taken out of the loop and it is being done anonymous, are we really like talking out of both sides of our mouths on that, and is it in fact the case that those people aren't going to be re-contacted and you won't have more information?

And I am quite skeptical about it myself.

DR. MURRAY: Now, you--

DR. MIIKE: Can I--

DR. MURRAY: Yes. We have two comments, and then I want to say something.

Larry and Kathi.

DR. MIIKE: My question to Dave is, is that what you say is a standard practice, or is that aberration?

Because I always come back to the point that we cannot develop rules aimed at the aberration. We have got to develop rules aimed at the majority. And then you develop special sanctions for the aberrations.

DR. COX: I am sorry to say that I think--okay--although I use it in a really extreme example, that it is more the standard rather than the exception. When researchers have an interesting finding, they pursue that finding, period. And it is not the patients' interests that are the ones that take primary concern. It is not the subjects' issues that take primary concern.

DR. MURRAY: Well, you know what, David? I realize this is kind of an awkward thing to say at an ethics commission, but that is wrong.

(Laughter.)

DR. COX: I agree.

DR. MURRAY: Okay. Then we will put that on

the record.

I mean, I think part of what we are designing are systems, as Larry points out, not that won't stop every possible malefactor from doing something wrong, although we would also like to have them in backup systems and come and try to nail those people and punish them for it, but we-- But that is wrong.

And I don't care how enthusiast you are about your finding, you don't violate the protections of human subjects to get those findings. I thought we established that about 50 years ago.

DR. COX: I agree. But the problem-- The reason-- One of the reasons why NBAC exists is because all those things are written down and they work not so well because people give lip service to it, but they don't act on it with respect to human subjects research in the way that there are laws with respect to animal research.

So I have no problem with a firewall, but I would like not to see, you know, a fire go through it. And right now I am saying that I don't think our society has ways of implementing the concept of the firewall because I think that it is too leaky right now, socially and culturally.

DR. MURRAY: Okay. I have more to say but I

want to give my colleagues-- Carol, Steve, Bernie.

DR. GREIDER: I just have a quick question for David.

Thinking about it very soberly, what proportion of scientists doing research do you really think would have that sort of a bulldog attitude, knowing that there are people concerned with the kind of research that might be going on; that there are concerns with their research; that they would ignore it anyway and go ahead? A serious re-estimation of what you just said.

DR. COX: All I can tell you, and this is printed, and it was the head of a very-- The president of a prominent scientific society who, at the end of his presidential remarks, made the comment that if it is the patient's consent or our right to do research, I will go for our right to do research. It was a public presidential statement that is written down.

MS. KRAMER: David, I am sorry, would you repeat that. I didn't--

(Laughter.)

MS. KRAMER: I couldn't hear you.

DR. COX: That if it is the patient's consent, informing the patients, or being able to have the sample to do the research, I will vote for going and doing the

research.

DR. GREIDER: But that is one individual?

DR. COX: It is one individual as the president representing the society.

MS. KRAMER: And he made that remark in public?

DR. COX: In public. A presidential address.

DR. MURRAY: I skipped over Kathi in coming up with the list of speakers. Kathi?

DR. HANNA: I just wanted to make-- I wanted to make the point, and this ties into what I think David is trying to say, and maybe there is a more diplomatic way of putting it, which is that I think that, for some, I guess--

The question I would ask is how truly useful would anonymized samples be? And I think for most geneticists they would say not too terribly useful unless they are doing molecular epidemiology. They are just trying to find the prevalence of a marker in a population. And that the data--the clinical data--that are tied to that anonymized sample are probably insufficient if they want to go further and try and find gene function, or do reverse genetics.

So I think that it is not so much that they

have some malicious intent to go and find these people; it is more that the system that is being proposed would render these samples virtually useless to them unless they could go back, and so they are going to have to go back and they are going to find a way to go back.

DR. COX: Sure. That is what I am saying. It is not enough saying that these are bad folks at all.

DR. MURRAY: Yes you are.

(Laughter.)

DR. COX: Okay. That is not what I am saying.

What I am saying is that if there are ways to get around the system, they will do it because of what Kathi said. It is because in order to have things of utility, the system precludes what they need, and they will go and find ways of bending the rules to be able to get that.

DR. MURRAY: Steve and Bernie.

MR. HOLTZMAN: I am a little puzzled. Speaking as an organization that spends $50-$100 million dollars a year on genetic research, we conduct all of it in an anonymized manner as we have been talking about and have no problem doing it in an anonymized manner. So I think we have to get a little more granular in our detail in what you are talking about, David.

It is one thing to say, "I want to go back and get more clinical information." It may not be sufficient for identifying the individual, hence it can still be in an anonymized manner.

If I collect it in the context of a research study, prospectively, I probably address the issue of re-consent, or rather re-contact, in that precisely because I thought it might be the case with respect to a subset that I found I might wish to go get more phenotypic information. Okay? All of those things are consistent with what we have been proposing now.

You are suggesting that the paradigm case is the instance in which you have phenotypic information about a research sample collected, let us say, in a clinical context with minimal consent--all right?--so the individual had no idea they were participating in this research, and that going beyond wanting to go back and get some more medical information that is non-identifying, rather the researcher has to get to that individual presumably because they have to get another sample. Okay?

DR. COX: Okay.

MR. HOLTZMAN: And to me that is not the paradigm case at all. I find that very infrequent.

And so I am not sure what you are referring

to, Kathi, when you say that what we are proposing doesn't work for the majority of genetic research. I just-- It is palpably false to me.

DR. COX: But, Steve, I will tell you why I believe that is the paradigm case, or will become the paradigm case.

It is because that it is not the-- My belief that what genetics does is it takes big populations and stratifies them down to smaller groups, smaller groups that are difficult to find; to go out and to recollect because those people are fairly rare. They are maybe 1 percent of the population.

So you maybe have 10,000 people but that 1 percent is going to get a lot of attention, a lot of attention. Everyone is going to want to jump on and study that 1 percent of the people that have a particular genetic make-up.

So those people are going to get inundated by being studied and you say, "Well, do it anonymous." Right? Or go out--

I mean, I don't understand that if it is anonymous how you, as a researcher, who do you talk to go and get the extra information that you need to design your clinical trial or to ask about relationships between

different types of diseases? What is the process?

I mean, I am open to the process. I guess what I am saying now is I don't see that we have a process for doing this and I don't--

(Simultaneous discussion.)

MR. HOLTZMAN: You said two different things. If my desire is to go back to do a clinical trial, obviously I have to find the body, the person.

DR. COX: Yes.

MR. HOLTZMAN: If, on the other hand, as we have proposed, a one-way permeable membrane, so that additional phenotypic information, or clinical characterization can be available, I can go back and say, with respect to Sample 71, where you gave us the following phenotypic information, it would be really useful, given what we have discovered, to see if you have any additional phenotypic information of the following sort. And get that.

DR. COX: And I am with you. Okay? So--

But the only dispute that we have, in terms of the paradigm, is that most, is most of the research going to be in the context of doing stuff that doesn't relate to sort of clinical trials that are coming up with therapies? Is that going to be the most useful research or is most of

the research going to be focused more on clinical trials that involves the body of the individual?

And I would argue that the future is going to be more in the direction of clinical trials involved in the body than anonymized stuff where you get a little bit more information to publish another paper. Again, that is just a personal opinion.

MR. HOLTZMAN: Yes. I think it is highly improbable because, when we have looked carefully at the economics of thinking of doing family studies as clinical trial populations, it just doesn't make sense. It doesn't work. You can't get the numbers and if you can get the numbers, then the labeling you will get for your drug is so small that you couldn't economically justify it.

DR. COX: If I can make one more statement in this regard, and it is a front-page article in the *San Francisco Chronicle* last Friday, and the headlines to it was "Big Biomedical Budget Push by Clinton."

And in it were some statements from Richard Klausner, of the National Cancer Institute, saying that in the next year he has a $3 billion dollar budget planned because he believes that clinical trials are really at risk in this country and that he wants to have more access to patients that want to be involved in clinical trials

and thinks that we need a new mechanism because that is the future of research.

So that, if he was correctly quoted, was the front-page news article from the head of NCI.

MR. HOLTZMAN: That is not inconsistent though. All right? If you are asking me whether or not there will be a pharmacogenetic basis for most selection of individuals for clinical trials, I think that is true. All right? But I don't think it will be necessarily familial or with respect to specific ethnic groups.

I don't want to get into the details here about snips and common variants, but you know what I am thinking.

DR. COX: All right.

DR. MURRAY: Bernie?

DR. LO: I just want to suggest that I think it would be really helpful, at least for me personally, if we could have some specific case scenarios. So I think David has some in mind. Steve, you clearly have some in mind saying that we can do a lot of really good research in an anonymous way. Kathi, you are concerned. I mean, to have that give flesh to the report would be helpful.

I also think it would help us as we deliberate because it is one thing to look at an abstract grid and it

is another thing to say, "Here are some typical research protocols that our best thinkers are saying are typical of what we are going to be facing." How well does our analysis fit?

DR. MURRAY: Right. I sense that issue has burned itself out, at least temporarily. Am I right?

DR. SHAPIRO: Could I just ask a question?

DR. MURRAY: Yes.

DR. SHAPIRO: Is the subcommittee decided on why you wanted two rows or three?

DR. MURRAY: I couldn't hear you.

DR. SHAPIRO: Is the subcommittee decided on whether you want two rows or three here? And I think it really makes some difference. And I don't have an-- I do have an opinion, but I would rather hear the committee's.

Or, Tom, if you think that is premature to even discuss now, by all means let us come back to it.

DR. MURRAY: I don't know. I don't think we have decided whether to have-- When you say two or three, I take it you mean-- We have all agreed, I believe, that where you have got an individual and there is no sort of group at risk, no community, "identifiable community," that that is Column 1, and we all agree that that has a certain set of rules.

The issue is, is there-- Where there is an identifiable community, ought we to do things differently? And do we need to have separate rows for--rows, not columns--rows for when there is no likely harm or some possibility of harm if, in fact, we intend to recommend some model of community consultation, rather than a kind of community veto? I thought it was a good question.

MS. KRAMER: Tom?

DR. MURRAY: Carol and Bette.

DR. GREIDER: I just wanted to say something because I think that Zeke was the one that was really in favor of having three rather than two, so I was trying to recreate in my mind what Zeke might say, just trying to remind myself what his arguments were for having three separate rows.

And it might have been because the sort of hoops that one would have to jump through would be different for Column 2, Row 2 versus Row 3. And that is why initially it was set out as three, to not put in the extra added burden where one isn't needed. I am just trying to think through why we initially had three.

DR. MURRAY: Right.

DR. GREIDER: And so that might be coming back around to the issue of a consultation or community

involvement might change somewhat how we would address that if it is less of a consent versus an involvement.

DR. MURRAY: Maybe I should just add something. When we heard the-- I can't remember the fellow's name from the last meeting.

DR. LO: Jack Killen.

DR. MURRAY: Pardon?

DR. LO: Jack Killen.

DR. MURRAY: Jack Killen, yes.

One of the things that Jack Killen helped me to understand better was that community consultation did not merely constitute an obstacle or a punishment. Quite the contrary, in fact. It often contributed in some very substantive but also sometimes subtle ways to the design of a particular study, to the ability to access subjects for study.

And maybe one possibility then is to simply say not have two and three, just have two. Just so where community is involved, to then recommend community consultation be undertaken. Now, I think that is, at this point, where I would lean, but I would like to hear what others have to say.

And Bette and Trish and Bernie and Harold are all in line. Bette?

MS. KRAMER: I just-- I want to understand clearly. When we use the term "consultation" as opposed to "consent," that implies that the community does not have the right to veto the project. Is that correct?

DR. MURRAY: That is my understanding, yes.

MS. KRAMER: Okay.

DR. MURRAY: Although I think practically speaking, if your community with whom you were consulting said, "This is a God-awful thing and we would recommend that no one in our community cooperate with it," you would be foolish to go ahead with it. So I think, in effect, there is a kind of veto, but we are not going to call it that. We are going to call it consultation.

DR. GREIDER: You might not be able to go ahead with it.

DR. MURRAY: You might not be able to go ahead with it.

MS. KRAMER: Right. And then I don't think we ever really addressed satisfactorily, at least not in my mind, what do we do when there are dissenting opinions within the community?

DR. MURRAY: As I think it is not an uncommon feature of discussions with the various groups involved with HIV research, which is where a lot of our experience

with community consultation comes. You deal with it.

MS. KRAMER: And we have the problem--

DR. MURRAY: Negotiate.

MS. KRAMER: --of the Ashkenazi Jewish women in the Boston area who didn't want to consent to a study.

DR. MURRAY: Right.

MS. KRAMER: That was nonetheless being done in other places.

DR. MURRAY: Right.

MS. BACKLAR: I think if you go back to the first section, where you have community, no potential harms, and community, potential harms, the reason you have to get those boxes into one is because who is going to make the decision about what those harms are other than the community itself? That they need to address it.

I mean, it is not going to be very good if it is an outsider who is saying to you, "Oh, no harm to you in this particular case." So that is the argument that I would have for putting them in one box.

DR. MURRAY: For putting them-- For not separating them?

MS. BACKLAR: For not separating.

DR. MURRAY: Yes. I think it is a good argument, Trish.

Bernie?

DR. LO: I think, to follow up on a point you made, Tom, I think we should try in the report to put forth a position that community consultation is a beneficial thing for the scientists and for the research. It is not a hurdle. It is not an extra administrative burden.

That, in fact, anyone doing genetics research, where some sort of ongoing interaction with patients or cooperation of the community is needed, would be foolish to try and plan a study without involving the community from the onset, it seems to me. So that this shouldn't be a conflict; it should be a congruence of interest.

DR. MURRAY: Harold, and then Larry.

DR. SHAPIRO: My main point was the same as Trish's so I am not going to repeat that. I just want to say one thing.

When I looked over the overview of this paper, as Kathi knows from the comments I gave her, I really objected to some of the distinctions that were made there between the researchers and clinicians. If I believe David, I may reconsider my position there. But, in any case, that we will come back to later.

DR. MURRAY: Larry?

DR. COX: Some of these researchers are clinicians.

DR. MIIKE: Just on the issue of community involvement in a community consultation, that has been going on for several years now, even outside the genetic area, so it is not really a controversial issue and I think it is--

Anybody who is going to try to do research nowadays is not going to do it on separate individuals, and I think it is just a practical and an unavoidable process that one has to take up anyway, so--

And I agree with Trish that it is that consultation process that decides whether the harm is minimal or severe and then, even if it is severe, whether the research protocol should go ahead anyway so--

DR. MURRAY: Carol?

DR. GREIDER: When we first went through this grid and tried to decide whether there were two or three, I was thinking about it in the mode that we first started discussing it, which is the community consent and how one was going to get consent from a community.

But the discussion that we had with Jack Killen last time, about his experience in the AIDS community and how they really had a very integrated

involvement of the community with the research, really dispelled in my mind the sort of confrontational us-them sort of paradigm that had initially been set out.

And so I have moved from feeling like we really needed to have three to agreeing with what other people have now said; that two probably would fit the bill if we can articulate very clearly the kinds of things that Jack was laying out for us as to why community involvement is important as a part of our report.

Because he was very convincing to me about that it is not a hoop to jump through, but rather it is an integrated process of doing the research.

DR. MURRAY: Thank you. I think I hear a consensus that we are collapsing Rows 2 and 3. Are there any strong descents to that? Are there any weak descents to that?

DR. GREIDER: But what about Zeke?

DR. MURRAY: He is not here so we will have him defend it, defend that decision to the group tomorrow, right? That would be--

MR. HOLTZMAN: I mean, I was with Zeke as well. As persuading as I am by Pat's line of thinking, the issue was, to the extent that it was a burden for the kind of study that palpably couldn't be stigmatizing--the

number of whorles on your finger or what-not--it seemed kind of onerous.

Again, I think just to echo what two of you at least have said, it is conceived of as consultation. It is a very different kind of hoop and, in fact, it is positive. I think what we have to acknowledge, however, is the pressure it then puts on us to give some guidance here to whomever we are asking to make these decisions as to what is a community? What is a--

Kathi, I think in the intro, used the collectivity definition that was found in the Canadian report. Because we are asking the IRBs to say is there a community involved, number one, and, if so, to go get some consultation. So I think we will have to give some pretty specific guidance.

DR. MURRAY: That is an important point. I-- We have-- I want to make two other observations.

One is that we may have achieved a kind of enlightened consensus, or we think it is enlightened--we know it is a consensus--about the value, potential value of community consultation in these kinds of cases.

My guess is that a lot of our scientist colleagues are going to have the same reaction that I am sure some of the scientists at this table had initially.

Be aware of that. Be prepared for it. We can do our best in the report to anticipate that and to explain, you know, why we think it need not amount to that. But there is going to be a certain amount of protests and a lot of education that will need to take place. Just be prepared for that, number one.

Number two is we are still going to have to, in line with Steve's suggestion, provide some substantive guidance--maybe also a little procedure--for figuring out when a "community" is involved. And maybe that becomes-- We may need to say that that is, in the end, that is an IRB decision whether there is a "identifiable community." At issue here, if so, one needs community consultation.

Trish has been waiting, and then David.

MS. BACKLAR: I am struck, as we discuss this, of how so much overlaps with our discussions in the Human Subject Committee.

And one of the things that I noticed when Jack Killen was here last time was that we did not address the issue of therapeutic misconception, which can occur here and which we want very much to make sure that we get this into this report, and that when communities do become involved they do start to muddle up; that between treatment and research and what may be an advantage to

them and what may not.

And we need to make sure that the researchers and the IRBs are very aware that, just because this is genetic research, the same issues obtain.

DR. MURRAY: David?

DR. COX: So I am very in favor of collapsing the three into two.

DR. MURRAY: Okay.

DR. COX: I think that while it may scare some people doing research to think that they have to have community involvement, in fact almost every paradigm that you look at that has been successful has involved community involvement when it had specific communities, whether they be ethnically defined, or even people with specific diseases.

DR. MURRAY: Could you help us by providing some examples of that--

DR. COX: So when--

DR. MURRAY: --to Kathi so we could actually put those, and name them, and describe them in our text?

DR. COX: Absolutely.

DR. MURRAY: Great.

DR. COX: So I am very--

DR. MURRAY: That would go a long way I think

towards making the point.

DR. COX: Yes.

DR. MURRAY: Bernie?

DR. LO: I also agree with collapsing the two columns.

I think that as we think about the report, I agree, there is going to be a lot of resistance among many scientists; this notion of community consultation.

I think, on the one hand, we do need to acknowledge that we talked at first; that both the scientists and the community people need to learn how to talk to each other, need to understand, you know, the languages the other people are speaking.

I think it is going to be acrimonious at first. I mean, the first couple of years are not going to be any easier than they were for the AIDS researchers. But you have got to get people to look at the long term, not the short term.

And then, to follow up on what Steve was saying, and Tom was saying, I think we should think through how far we want to go with this. I think we should do more than just say, "Do community consultation." We should at least, it seems to me, identify key issues that need to be worked out to make that meaningful. And

maybe this is just a process.

I don't think it should be left up to individual IRBs. I mean, they are going to all stumble around in the dark. I think the NIH and other national organizations need to take some leadership in calling some national meetings to achieve some guidelines on how you do community consultation. I am not so sure we need to do that, but I think we can sort of say someone else needs to do this.

You know, my own feeling is that we don't have to settle all the issues. We just have to point people in the right direction. If we point them in the direction of saying community consultation is a good thing, here are some issues that you need to address to make it really work, here are some procedural things that we think might help get scientists thinking about this.

There is going to be a lot of re-training. I mean, a lot of geneticists just really aren't that good talking to people and that is what this is about; talking and listening. They are going to have to re-train themselves.

DR. MURRAY: Thank you, Bernie. This seems a good time to take a 10-minute break.

If anyone wishes to do public commentary,

would you please tell Patricia Norris. Pat, would you raise your hand so that people know who you are? That is even better. Thank you, Pat. Would you please let Patricia Norris know that you would like to do so.

And we will see you--I have about 3:33 p.m.--so we will see you at about 3:45 p.m. We will start then. Bye-bye.

(Whereupon, at 3:33 p.m., there was a brief recess.)

NEXT STEPS

THOMAS MURRAY, Ph.D.

DR. MURRAY: We have an hour and a quarter.

We have one public statement scheduled to be provided, so we will need to reserve five or so minutes for that. And I think in all curtesy to that--and to that person--we should not wait until the end but try to do it, in fact, about the scheduled time, which was 4:30 p.m.

Among the things we need to do before we leave today are decide how we want to use our time tomorrow in the full committee.

If you look at your agenda for tomorrow--if you don't have it handy I can remind you what it is--we have--

Harold will welcome everyone at 8:00 a.m.

We basically have until 9:30 a.m. to conduct our preliminary discussion.

We have two individuals, Susan Old from the National Heart, Lung and Blood Institute and Patricia Barr from the National Action Plan on Breast Cancer, who are expected to make comments and engage us in conversation. And that will go on until about a little after 10:00 a.m.

After the coffee break, we will then have until 11:30 a.m., which is the time for public statements.

At that point, we are finished for the day, at least as our subcommittee, so we need to use that time well tomorrow.

So as I calculate it, we have for ourselves roughly an hour and 20 minutes, and then about another hour and 10 minutes. We have about two and a half hours to do our presentation, when we are not actually also engaging scheduled speakers. So we want to use that time well.

And before we quit today, we need to figure out who is going to, how we want to use it and who do we want to lead the conversation. Do we want to divide up responsibility for different issues or different portions? So I will give you that warning.

Eric Meslin has also asked me to raise a couple of points, and I will do that.

One is whether or not--I think we did address this--whether or not we want to have a specific model consent form that we endorse or whether instead we should talk more generally about the elements of appropriate consent.

My recollection is we talked about it--we discussed that--and decided not to press a specific model consent form. Is that correct? Does everyone agree with that? Not as a statement of fact, but as something we actually would want to do.

MS. KRAMER: I think we had raised the possibility of maybe including in the report four or five examples of consent forms that had been presented to us. I don't think we resolved it, but we raised that possibility.

DR. MURRAY: Yes. I think we did talk a little bit.

Steve, did you-- No.

Carol?

DR. GREIDER: I just wanted to mention that it was pointed out to me by Elisa Eisman that, in her final report on the stored tissue samples inventory, she has

collected a large number of sample informed consent forms. And I don't know if anyone else got this final report, but there are a number of them in there if we want to look through those to continue the discussion.

DR. MURRAY: Right. Yes. I got my copy about 10 minutes ago when Elisa handed it to me, so I haven't had-- And she pointed out that there are those examples of consent forms.

And we have the material from the National Action Plan and from the Primer(?) Conference and some other materials that we may wish to at least certainly refer to.

Bernie?

DR. LO: I guess I would be in favor of not trying to develop a model form because I think that is going to change over time and it is going to go through iterations. People are going to test forms, find out some things work, and some things don't. And I think we are better off sticking to the goals and principles rather than specific forms.

DR. MURRAY: I don't hear any descent from that position.

Steve?

MR. HOLTZMAN: Just you can go one step beyond

goals and principles to the elements.

DR. MURRAY: Yes.

MR. HOLTZMAN: Right? I think it would be very useful. The elements of the consent that are important.

DR. MURRAY: Yes. The consensus I thought I was agreeing with was something short of designing or voting on a specific model consent, but rather talking in somewhat more general terms about what consent forms ought to be like.

DR. MIIKE: There is also a practical obstacle, which is that we are suggesting general consent. I mean, the consent varies according to the situation.

DR. MURRAY: Okay. So I think we are in full agreement on that, and I feel very comfortable defending our position on that.

Another point that Eric has asked me to raise with you is to consider whether to regard the stored tissue report; to publish it first as a "interim report," with a comment-limited, specified comment period, or whether to publish it, I presume alternatively, as our report?

Now, I have a view on this, but I want to hear what the other commissioners say.

DR. MIIKE: Can you say that again. As an interim?

MS. KRAMER: Can you say that again.

DR. MURRAY: Eric, why don't you--since you proposed this--why don't you describe what you have in mind?

DR. MESLIN: It occurs-- At least it occurred to me and some others that a report of this import, one that is being waited on by a number of organizations and which we have promised, cannot hope to enjoy the input from all possible commentators and that, since there is no specific deadline to get it out, except for as soon as we can in the highest possible quality fashion, that it might be useful to disseminate an interim or draft report which contains all of the deliberations and our recommendations and allow for a period of public comment, to be decided on as a reasonable amount of time, that would allow as many people as possible the opportunity to read it, to think about it, and to provide whatever comments or input that they felt appropriate.

That public accountability model I think is very useful, but it also I think provides an opportunity for the commissioners to hear views that they might not otherwise have heard by individuals who could not come to

the meetings, who weren't able to provide written documents. These would certainly be seen as comments and would be considered before the commission issued its final report shortly thereafter.

MS. BACKLAR: I think it is a great idea.

DR. MURRAY: Harold?

DR. SHAPIRO: I also am strongly supportive of that idea. And we have a model which I think worked very well and that is the Canadian group, what is called the Tricouncil, which publishes various drafts up on the Web, and it was extraordinarily improved from draft to draft, at least as I feel it.

And I think it was mainly comments from people who hadn't had an opportunity to be at the meetings, hadn't fully understood exactly what the recommendations were until they could see them laid out that way. And so there is an easy way to get it around now. And I think it would lend an awful lot more credibility and probably increase the quality of the final document.

DR. MURRAY: Bette?

MS. KRAMER: Well, it would also, if we in fact go forward with the public opinion survey, enable us to incorporate anything that we learned from that in the final report.

DR. MURRAY: Then the final report would be maybe in our lifetime. I mean, it is a while before I think we are going to have a public opinion survey to incorporate.

MS. KRAMER: No. I am sorry. I don't understand. Which is going to be further into the future.

DR. MURRAY: The wait until we get the results of the opinion survey, while I think it is within our lifetime--

I guess I don't have the same enthusiasm for doing it as an interim report. I understand the arguments, and some of them I find pretty good for doing it that way. People are looking for guidance from us. And are we going to say, "Well, here is our guidance, but it is not really our guidance because it is only an interim report and we might change things."

And it will mean, quite frankly, that a considerable portion of our energies after this report, when we are working on the next one, will have to go back and revisit this report. And I am very concerned about the time and the attention of commission members so I think there is a trade-off that we need to be conscience that we would be making if we chose this strategy.

DR. SHAPIRO: Tom, I think you are right. It

is a trade-off. But, one, I think the staff can be very heavily involved in dealing with this at the response level, and then bring some changes to us if there are any at that time. And, you know, I think your point is a good point. I mean, I certainly understand it. But I think on balance that we would still be well served.

I don't think we should give a long period for comments. I think we give a relatively short period for comments. I don't know what that means. I haven't thought that out. But it is weeks, not months, that I have in mind. But I understand the point. It does cost some--

DR. MURRAY: Let me actually mention one other virtue of doing it as an interim report. People are more likely to read it if there is a chance that they can actually make suggestions that will help shape, that will help modify it. That-- I have to grant that as maybe one of the strongest arguments in favor of doing it as an interim report.

DR. COX: Yes. And, Tom, that is actually the point that I was going to bring up. I am in favor of an interim report, but for that purpose. Because if Eric Cassell was here he would call it education. And by calling it an interim report, you are going to get many

more--hopefully--people involved.

I am pessimistic in terms of how useful the input is going to be because it is going to be not from people we haven't heard before, but it is going to be from all of the people we have heard from before, and we already know what they have to say. But that perhaps at least it gives the opportunity of education and having more people involved.

So I quite agree with your points in terms of the downside--and for me it is a fine line--but I am more in favor of it being an interim primarily for this education part.

DR. MURRAY: Carol?

DR. GREIDER: I agree. I think that if we can really publish it on the Web where people could really have access to it, then it would be a very useful thing to be able to get comments back.

I mean, I always circulate anything before I publish it to colleagues to get comments from them.

If we couldn't publish it in something that is quite that accessible, I would be less in favor of having a draft report that is just a paper report that is going to be difficult for people to get a hold of anyway.

DR. MURRAY: Bernie?

DR. LO: Yes. I will just put my vote in for having an interim report and getting feedback. I think patient advocates and the scientists are going to have to live with the report, so we should give them a chance to give us some feedback.

DR. MURRAY: If we publish it on the Web, that will certainly make it available to people with access and sophistication about getting--using--the World Wide Web. Will that get to all, you know, most of, if not all, of our relevant publics? To scientists I expect it would. Would the consumer groups, public groups, be able to do that?

DR. LO: I think a lot of the people would be able to, sure.

DR. MURRAY: Yes.

DR. SHAPIRO: We order pizzas on the Web.

(Laughter.)

DR. MURRAY: We order pizzas on the Web.

MS. KRAMER: You know, Tom, I suspect if there is a group that wants to pass it around to their particular audience, they can always-- There is nothing to stop them from publishing it themselves or printing it.

DR. MURRAY: Right. Right. Well, this sounds like I seem to be the only one who has dug-- I haven't

exactly dug my heels in. I am being dragged along though.

I think it might be well then to mention this tomorrow to the full commission, do you think? I would rather not have it take up part of our brief substantive time, but as we talk about strategies for publication, if we could mention this as a possible strategy that, if it worked well, I suppose could be a model for other reports where it was equally suitable. I am not making a judgement whether it would always be suitable, but I am--

Okay. I think actually we have gotten an answer to that question then.

DISCUSSION OF TISSUE SAMPLES REPORT (CONTINUED)

THOMAS MURRAY, Ph. D.

DR. MURRAY: Let us get back to the substance of the report, shall we?

Trish?

MS. BACKLAR: I am not sure that I made myself clear about one thing in terms of the Tissue Sample Report, and that is I have a concern about cutting out people from getting information about research that-- I am very concerned. Just as though it--

As a private person, if some of my tissue was used for research, I would want to know if something was important to me, so another reason for being very cautious

about a firewall. That is all I am saying. I don't think I made that clear before.

DR. MURRAY: Let me see if I understand your point. As I-- And let me tie it into-- Because it is one of the things we need to talk about. There are two circumstances under which people may want to reach this-- what we have called a--firewall. We probably need a better metaphor, but that is the image we are stuck with at the moment.

One of them is this sort of-- It is David's cadre of researchers who really, really want to find out who those people are.

DR. COX: The Spice Girls. They really, really, really want to know.

DR. MURRAY: The Spice Girls.

(Laughter.)

DR. MURRAY: Well, listen I was in England for a week in December and they are already passe so how quickly-- How fleeting is fame?

So that is one motivation, right?

The second motivation though is one that I heard from the mini-hearing participants in Cleveland--and I gather it wasn't just in Cleveland that this was articulated--that there is a feeling on the part of people

who contribute to research, by whatever means, including tissue, that, if it is possible for that research to benefit them, then it ought to benefit them.

That they sort of made a kind of contribution. If scientists learn something about them that they ought to know, they would like to have the opportunity to find out.

I was surprised at the intensity of that feeling. Now that exists I must say with an equally intense desire to protect privacy.

MS. BACKLAR: That is what I am referring to.

DR. MURRAY: Yes. I thought it was that latter.

MS. BACKLAR: Right.

DR. MURRAY: Right.

MS. BACKLAR: I just wanted to make sure that I said it.

DR. MURRAY: We need to talk about that. I mean, if our recommendation said that this must be a firewall that is as absolutely unbreachable as human ingenuity can make it, then we have eliminated both those breaches, or we try to eliminate all those breaches if possible. Do we want to set up something less than that, at least in certain circumstances?

Now, my reading of the summaries of the Primer meetings and the National Action Plan on Breast Cancer meeting is that there was some sentiment there as well; that--you know, particularly of this latter sort, the kind Trish was concerned about--that that ought to be possible when it was really, really important and clinically relevant, or some other intimate personal way relevant to the subjects. So we need to address that.

Bernie?

DR. LO: Yes. I think it is a really important topic, particularly in the context of anonymized versus anonymous samples; that we have in this grid the possibility of having samples that are anonymous to the researcher but linkable to somebody else.

And so it is not a matter that you can't contact the person because you simply don't know. You could if you kind of could work backwards through the system. But we have constructed a system that says, "It is not going to be permissible to do that."

And it seems to me there are a lot of reasons why you might want to get back to the patient. One is just the patient is curious, the patient wants to know, the patient thinks that is part of the arrangement of donating tissue.

There is another situation in which clinically the researcher, as scientist/clinician, thinks it really is in that patient's best interest in that you have made a discovery which is far more powerful than you had anticipated, so rather than just a slight stratification, you have got a combination of genetic findings that predicts with--whatever--80 or 90 percent likelihood that someone is going to develop a serious form of cancer. And you didn't anticipate quite that at this stage of your study.

I think the pressure on the physician/scientist to say this has clinical importance and I would like to at least offer the patient the option of learning it is going to be very powerful.

Again, we saw this in the AIDS epidemic where there was a lot of AIDS testing early on that was done on anonymized samples, samples that were taken for other contexts and then stripped of identifiers. And you found, you know, 5 percent of people were HIV positive.

And you could have contacted them had you allowed the system to work. They were contactable at one time. But for a whole lot of reasons, many of which I actually argued persuasively at the time, you chose not to do so.

I just think it is an issue. It is a dilemma. It is a real dilemma that we need to sort of sort out. And I think a lot of the concerns that were present in the AIDS epidemic, where you really needed to get an accurate picture of the epidemic--you were afraid of biosamples, scaring off people who were at highest risk--really don't apply to the type of DNA-based research we are talking about.

So the values that stay are sort of the convenience of doing the research versus either the wish of the patient to be informed or kind of a beneficence-oriented argument that it might be in their best interest to know.

And I just think the idea of a firewall sounds neat because it seems to solve some problems at the front-end. It actually makes, creates dilemmas after the research is done and you get--what we all hope for--smashingly positive results.

DR. MURRAY: Steve and David.

MR. HOLTZMAN: I just have a quick comment that struck me when you said the kind of DNA research we are talking about.

I thought this committee agreed that what we were dealing with was medical research on stored tissue

samples, not just genetic research. All right? And I think that is just-- And I think we are going to have to come back to that issue. Just I think that is very important because three times I have heard that in the last half-hour.

DR. MURRAY: Let us nail that one down.

MS. BACKLAR: Yes.

DR. MURRAY: Do we agree with Steve that-- I mean, I think practically I can't find any other way to think about it. If we are going to come up with a set of policies and practices about research of stored tissues; to say they only apply if the research is "genetic" and not otherwise seems like a-- It seems like we are doing no favor to anybody involved in the process.

Is that-- Now, if there is any disagreement with that, please let it be known.

DR. GREIDER: I agree with Steve.

DR. MIIKE: Say that again.

MS. BACKLAR: I agree.

DR. MIIKE: Are we saying that it is tissue research? But a lot of the concerns that we have been discussing don't apply outside the genetic area.

MS. BACKLAR: But they might.

MR. HOLTZMAN: A lot of the concerns we have

been discussing don't apply within the genetic area.

DR. MIIKE: I am sorry. What, Steve?

MR. HOLTZMAN: A lot of the concerns we have been discussing don't apply within the genetic area. They apply-- Most of the concerns we have, have to do with a set of findings about biological information that pertain to issues like predisposition, stigmatization, et cetera, et cetera, which cuts across genetic and non-genetic.

I mean, if we are going to--

DR. MIIKE: But it is not because I have a piece of bone that people are looking at; it is because of the genetic material within the bone. I mean, you may disagree that stigmatization has nothing to do with genetics, but that is what we have been discussing.

MR. HOLTZMAN: Well, it actually--

DR. MIIKE: You know, like-- Well, let us take a ridiculous example. I notice that the definition of tissue includes feces and urine in our draft.

DR. GREIDER: It won't.

(Laughter.)

DR. MIIKE: Okay then. There you go. There you go. Then why are we talking about tissue outside the genetic context?

DR. COX: I think there is a compromise

position here and the compromise position is--I think this is what you are sort of trying to nail down, Steve--is that we had agreed that genetic information isn't inherently different from other types of medical information. That is-- I recollect that that has definitely been agreed to.

Having said that, it doesn't mean that there are not situations where genetic information has some different implications than other medical information, but that we don't--

(Laughter.)

DR. COX: We don't want to-- Is that better? Okay. I don't want this-- I am scared of them.

DR. MURRAY: Just remember all those Grateful Dead concerts, David. They were right up to the microphone.

DR. COX: So I agree with you, Steve, but I don't think we want to carve it out, you know, and just be talking about genetics. But, on the other hand, there can be special situations and we highlight those if we see that they exist.

And that was exactly the point, Tom, that I wanted to make in this context of the firewall, too, is that it makes us feel really good if we have a single box

we can put everything in and close the lid. But that is not the way life works.

So that if we could put most of the things in the box, but then delineate certain exceptions that we think are likely to happen, and we acknowledge that they might happen, and we say-- And if they-- And so these are things we have to think about because the box isn't perfect. Then I think that is reality.

And so I am more than willing to go with what you say, Steve, but then if there are specific examples that appear, you know, special for genetics, just highlight those. But it is not to say that genetic information is separate from other medical information.

DR. MURRAY: We may be flogging this more than we need to. I mean, I think if our report-- We would say in our report that we just-- We explored this issue of the use of human tissues in research because of the ability to extract large amounts of genetic information potentially from that tissue, and that is part of the opening of the report in fact.

We could then simply note that it would make sense to, you know, since tissues can--

DR. MIIKE: Aren't we the Genetics Subcommittee?

DR. MURRAY: Pardon? We are the Genetics Subcommittee.

I guess all I want to do is not ghettoize genetics and also not make people labor under two, sort of two radically different systems for not good reasons.

So we might just say, you know, we think what we are proposing would make sense as a general set of principles and procedures governing research with human tissues, even though we come into this from the genetic angle. I would I think be content to say that much.

DR. GREIDER: Why do we need to say that there are special instances in which genetics is different? That is what you just proposed, David.

DR. COX: I am saying that, if people want to say that, then we need to define the special instances. And I would give an example myself of what I would consider a special instance in terms of being different. And it is a quantitative rather than a qualitative difference. And it has to do with what the predictive power is.

So I would say that if somebody-- If genetics had a 95 percent predictive power, where most other information had a 25 percent predictive power, genetics is different. And it is different because it is more

powerful in that specific instance of prediction. Not overall, but in that one instance. There can be specific examples that the--

The specific example--it is a well worn one, but to make the point--is Huntington's disease. Okay? The power of genetic information in Huntington's disease, when you know that change in the DNA, is an unbelievable power.

DR. GREIDER: What about the predictive nature of somebody that is infected with HIV virus? There is a very high predictive feature there and you wouldn't say that that is a genetic. So there are predictive powers that aren't necessarily genetic.

DR. COX: Oh, no. And I agree with that. All right? So I am not saying this is unique to genetics, but it is unique to the specific case.

MR. HOLTZMAN: It is unique to a monogenic highly penetrant disorder.

DR. COX: Bingo. Thank you.

MR. HOLTZMAN: Okay. Which, when you think about HIV, is monogenic, a single genome, if you will--all right?--and highly penetrant.

DR. COX: Exactly.

MR. HOLTZMAN: So the point is--

(Simultaneous discussion.)

DR. COX: --is an example.

MR. HOLTZMAN: --and what we are concerned about-- What I always find very useful heuristically is to forget I even knew the word "genetic" and ask what am I concerned about? All right?

And you find that there will be cases where the analyte is DNA, the analyte is RNA, the analyte is protein, instances where it is heritable, instances where it is not heritable but it is communicable, instances where it is DNA but a somatic mutation. All right?

DR. COX: Exactly. And you use those examples.

MR. HOLTZMAN: And I think that was the whole conversation that we had in the meeting which Larry wasn't at when we talked about, yes, we are a Genetics Subcommittee--all right?--but all of it couldn't be instances of the papers that Zeke brought forward. And I think there was only one out of the six or seven which was a genetic study.

And the point he was trying to make heuristically was the kinds of studies that are undertaken and where the ethical engine could get going of concern is not specifically genetic. And I thought we had come to

that conclusion. All right?

I don't mean to flog a dead horse, but--

DR. MURRAY: That is okay.

DR. GREIDER: So, Larry, why do you want to limit it to genetics if not limiting it to genetics is more inclusive, would include more things.

DR. MIIKE: No, no. I mean--

DR. GREIDER: What is the reason to--

DR. MIIKE: I am not limiting it to genetics. I am opposed to saying that the issue that we are looking at--tissue sample research--is separate from genetics, and it is not. To me it is essentially the same. I mean, the concerns that are being raised here.

Are you telling me that the future of research is diverting away from the genetic basis of the tissue samples? Isn't that where the research is heading?

I mean, you know--

MR. HOLTZMAN: I think research is--

DR. MIIKE: --look at me as the lay person. And you are trying-- You scientists are telling me our concern about tissue samples is not primarily genetics or not solely genetics. Convince me about that.

MR. HOLTZMAN: Whose concern? That the individuals, the lay people's concern or-- Whose?

DR. MIIKE: No, no. What you folks have just raised, which is that this is a tissue sample issue; it is not a genetics issue. I am saying it is a genetics issue within the tissue sample subject.

Or have I just been hearing everything wrong just lately?

DR. GREIDER: I think that it limits what you will discuss about something to say solely that it is a genetic issue. It is a biology issue, which is greater than just the term "genetics."

DR. MIIKE: Well, isn't that what the concern here is?

MR. HOLTZMAN: I think you just crystallized it. All right? If what I was proposing to do was to go in and analyze whether or not the tissue had an X and Y chromosome or X and X chromosome, I don't think there would be a heck of a lot of concern being generated and people wouldn't be exercised about the issue. So there is an example of genetic research which is non-concerning.

On the other hand, take the HIV example. If you are going into tissue and you are finding out something that is non-genetic, it does generate a concern. Okay?

So the only point we are making is that, when

one starts to think about it, that the sources of concern all relate to characteristics of the nature of the information you are generating and there are implications for the individual.

DR. MIIKE: But, Steve, what I am saying is that, to me, that goes all way over my head. It makes no sense.

MR. HOLTZMAN: Well, I am sorry.

DR. MIIKE: No. I am--

MR. HOLTZMAN: I mean--

DR. MIIKE: The example you use about what is the relevance of HIV to tissue sample research?

MR. HOLTZMAN: What is the relevance of HIV?

DR. MIIKE: Yes.

MR. HOLTZMAN: I think--

DR. MURRAY: Bernie, I think--

MR. HOLTZMAN: Bernie just went through it and gave an example.

DR. MIIKE: Okay. But it is because it has affected the genome, right?

MR. HOLTZMAN: No.

DR. MIIKE: No?

DR. MURRAY: Bernie?

DR. LO: Well, maybe one way to try and

resolve this is to try and say that there are certain types of research that raise profound ethical concerns. They have to do with telling someone who is relatively asymptomatic that we can very strongly predict what is going to happen to you in the future, and it is going to effect other people as well, and there could be some stigma and discrimination.

DR. MIIKE: Right.

DR. LO: Those are not exclusive to genetic information. And the HIV example and cancer and other things are examples. But I think what we want to say is that some of the concerns are genetic examples and we expect there will be other genetic examples.

And to follow up on Larry's point, to the extent that there will be more and more genetics research being done, we want to kind of anticipate those problems.

But the issues we are raising are not specific to genetics; they spread over a whole lot of other--

MR. HOLTZMAN: And that is the point. What you just did is to forget you understood the word genetics. What are the characteristics--almost the social characteristics--that we care about?

DR. MIIKE: No, no. I agree with that. I mean, I agree with that. But I am looking at this-- I

mean, when we talk about genetic information and the implications of that information, it is like other medical information. I agree.

But I am looking at the specific issue of tissue samples. Yes.

MR. HOLTZMAN: Right. There are all sorts of analyses that are going to take place on these, Larry, which are not just looking for heritable genetic mutations. You are going to be looking at somatic mutations, you are going to be looking at proteins, you are going to be looking at any number of different things. You could be getting all sorts of kinds of information out of this that are not--

DR. HANNA: Steve, I think-- You keep referring to this. I think you are misinterpreting what I am having a problem with and perhaps what Larry is having a problem with.

I don't think either one of us is saying we are only talking about heritable mutation or family studies or, you know, linear transmission of disease.

I think we are talking about the fact that DNA is stable in tissues. Other forms of medical information that you can get out of those tissues is not necessarily stable. And I think what-- It is-- Perhaps there is not

as much disagreement as everyone thinks there is, but it is-- Maybe we shouldn't say "genetic;" maybe we should say "DNA-based" information.

MR. HOLTZMAN: But-- But-- Now you are hanging the issues of the public policy on the stability of the analyte, which I really-- I am confused, Kathi. I mean, why is that important? I mean, if I flesh-- More and more of these samples are going to be frozen. All right? And so in fact you will be able to recover other analytes as well. All right?

With respect to urine, which you said doesn't belong in the report, I think maple syrup urine is a genetic condition which one can go and look at urine and, what is more, one can get proteins out of urine and be able to-- So in fact, in a relevant sense, it is tissue.

I mean, what we are talking about, or what we care about, and where the engine is going to end up going has to do with issues of informed consent, issues of potential predisposition, issues of stigmatization--all of those things--and the notion of one's relationship to a sample. And all of those issues are not a function of the analyte, are not a function of the nature of the test.

DR. HANNA: Well, I think that-- I don't think that the report so far is suggesting that these

issues are unique to genetics. I mean, in fact--

MR. HOLTZMAN: I am not--

DR. HANNA: --if you say repeatedly that they are not unique to genetics, then I would think your bases are covered. But I think maybe--

And I have asked for four months for somebody to please write, explain, give me a reference--or whatever--that I can incorporate that will counteract, you know, the tenor and the tone of what is disturbing you.

MR. HOLTZMAN: Well--

DR. HANNA: I can't-- I am not convinced, in a way that I can sit down and write it, so--

MR. HOLTZMAN: And that is why-- I am not so much referring to the report. It is just that I picked up a comment, or twice in the last 15 minutes that I was here--and I got here late and I don't know if it was discussed earlier--but I had thought that the committee had discussed the issue and had come to a position. That is all.

DR. HANNA: But the position has to be justified in the report, and we don't have that.

MR. HOLTZMAN: We--

DR. GREIDER: So, I mean, Zeke pulled out some very nice examples of where tissues were used

prospectively, retrospectively, and we had them all in our book, and he had labeled them. And, as I recall, most of those were not using genetic information by any of these definitions that we have given.

So if we can go back to those actual research papers that he pulled out for us and look at what are the issues that are discussed there--unfortunately, I don't have them with me--but my recollection is that most of them didn't have anything to do with genetics. That there are issues that go beyond the genetics that are important in tissue.

DR. MURRAY: David?

DR. COX: This is a very interesting discussion because everybody is right. And it is the relative weight that people are putting on these issues.

Of course there are papers that have been published in the past with respect to tissues that don't have anything to do with genetics. All right? And of course it is true that one of the reasons why our government and the public is excited about medical research is because they believe that genetics is going to offer something real special.

So it is where the relative balance is. And for this commission to say it is all in genetics is a

mistake, but for this commission to say that genetics isn't where the action is, and isn't where the excitement is, I mean, we would get laughed off the stage.

DR. MURRAY: I didn't hear anybody who wanted to say that.

What I-- I have a very simple-minded view of this, which is--I don't know--I think mainly that I want to keep things as simple as possible. And so if we are going to articulate a set of principles and recommend a set of practices about how to deal with research in human tissue samples, I would like to just do it as that.

The door which gets us in there is genetics, and clearly a lot of the action in the future will be in genetics, but probably not all of it. But all that is fine. I just want to keep it simple.

I think we do a favor to everybody involved if we don't segregate and sort of say if you are using this sample for genetic research these are the rules, but if you are using it for something else these are the rules. I think that would be a disaster.

DR. COX: Okay. But, Tom, then having said that--I am in favor of keeping it simple, too--but this is the point I made before and I will make it again now is that it is unlikely that we are going to have a single set

of rules without any exceptions that takes account of everything.

DR. MURRAY: Oh, yes.

DR. COX: And you will get--

DR. MURRAY: No argument.

DR. COX: And if there are some clear exceptions that we can easily identify, then I would rather face them up-front very clearly rather than pretend they don't exist.

And I am not implying that people are trying to pretend they don't exist, but I think that in an effort to keep things simple sometimes we don't want to think about the exceptions.

DR. MURRAY: Well, there is simple and rigid.

DR. COX: Yes.

DR. MURRAY: And there is simple that acknowledges the fact that, in an effort to keep things relatively simple, you may do injustices. And so you try to build in some probably procedural means for responding to obvious inequities.

DR. COX: Exactly.

DR. MURRAY: This is a problem that you find--and one finds--in the law all the time.

I have some good articles if anybody wants a

reference on it. Steven Tillman(?) has got a wonderful piece on the tyranny of principles about a decade ago and he sent a report on this.

I think we are okay on this. Now, there are differences of sentiment here. I am not sure there is a lot of difference at the end in the substance.

Kathi needs a reference. I will give you a reference. I have the reference. I will give you the article that I hope will at least articulate one view of this.

We have-- It is almost time for public testimony, but what I would like to do is spend a few minutes getting us back to the concern that Trish raised; that is, what happens if there is information generated, through research on tissues which had been used anonymously, that might be clinically relevant for the person who was the source of those tissues?

Just to recap where we have been on this. I mean, Zeke-- I think we are here articulating Zeke's position if we say--because I think he said it again today--he would like to see a pretty impenetrable or one-way penetrable wall, not being able to go back, partly on the grounds that if it is-- You know, at least a couple of grounds.

Number one, the kinds of "clinically relevant information" generated in research laboratories are not clear level, you know, they are not diagnostic tests as we normally understand them and standardize them, so there is some ambiguity there, number one.

And, number two, if it is really important it gets published and it gets disseminated to the health professionals taking care of these patients and so they will get the benefit; they will just get it that route rather than walking, rather than by breaching a firewall.

Am I right? Those are two kinds of standard arguments?

Now, over against that we have the kinds of concerns that Trish has tried to articulate, I think, Do you-- Why don't you pick up the thread, Trish.

MS. BACKLAR: If there is something wrong with me, I want to know about it. If there is something wrong with me and might affect my family, I may want to know about it. I certainly would want to discuss it with them. But the simple thing, if there is something wrong, I will want to know about it.

DR. GREIDER: But that isn't necessarily true for everybody.

MS. BACKLAR: That is correct. I didn't say

it was. I said it was a private--

DR. GREIDER: So that is the issue that you have to deal with, is that some--

MS. BACKLAR: Correct.

DR. GREIDER: --people feel that way and some--

MS. BACKLAR: So I want to put that on the table because I don't think that I am the only person who believes that and, in fact, Bette-- Oh, no, it was actually Tom, I think, who substantiated that point of view--

DR. GREIDER: But if you allow walking--

MS. BACKLAR: --from the focus groups.

DR. GREIDER: If you allow the walking back, because there are people that do want to know, then what about those people that really don't want to know? So that is the danger of walking back is that there are people who would--

MS. BACKLAR: I thought that--

DR. GREIDER: --want to not know.

MS. BACKLAR: I thought that--

DR. GREIDER: So where does the weight come down to--

MS. BACKLAR: Wait, wait, wait. I did think

that was why we did all agree that the consent procedures were--the consent refusal procedures were--very important in the tissue issue so that if you refuse it doesn't come back, but I don't-- I would not want to be cut out because of some procedure that was put in place that didn't give me the option.

DR. GREIDER: What about the already-collected samples where there was no such--

MS. BACKLAR: Well, I can't live retrospectively.

DR. GREIDER: Well, I mean--

MS. BACKLAR: I am not--

DR. GREIDER: --we are dealing with that though.

MS. BACKLAR: Right. Well, obviously I can't alter that in which there is no way back. I mean, it is not--

DR. GREIDER: There is a way back.

MS. BACKLAR: It is like Orpheus and Eurydice. If you look back it is over with.

DR. GREIDER: Well, there is a way back--

MS. BACKLAR: There is a way back?

DR. GREIDER: --currently, but those people haven't said whether they would or wouldn't want to be re-

contacted. That is the issue. And if you re-contact them, you might be giving them information that they don't want to know and you are already--

MS. BACKLAR: You are giving them the option of saying yes or no, you see. You are giving them the chance to say yes or no. If there is a way that you can go back, you are at least--

DR. GREIDER: Not if you have a piece of information about somebody and you are contacting them because you know this information and you want to get more information from them. Just by contacting them, that is giving them some information.

DR. MURRAY: Harold wanted in on this.

DR. SHAPIRO: Trish, just ask the question. You are concerned with future samples. Do I understand that correctly or not?

MS. BACKLAR: Yes.

DR. SHAPIRO: And in all cases, therefore, there is individual consent, according to this.

MS. BACKLAR: Right.

DR. SHAPIRO: Therefore, does your issue come down--I am asking a question--to what we provide, what the nature of that consent form is in this respect; that is, whether a consent form contains some options in this

regard, or not?

MS. BACKLAR: Well--

DR. SHAPIRO: I am just asking a question. I am not--

MS. BACKLAR: No, no. I am actually not going to quite answer your question. It seems to me evident that one should have those options there.

DR. SHAPIRO: Okay.

MS. BACKLAR: I don't-- I have no difficulty with that.

I think that Carol has brought up something which is significant in this and that is that, if something was found out in tissue that was already collected that might benefit me and that I had not been able to give my specific consent to and there was some firewall built, I would be very concerned that I didn't have access to that.

DR. MURRAY: David, and then Bernie.

DR. COX: So, to say it in a slightly different way, but the same point that Trish is making, as a physician if I find out that my-- My oath as a physician is to do no harm. If I find out something about a person--that they are going to die and I have a treatment that can keep them alive--I have a real conflict

if I have a firewall that says I can't contact that person.

DR. MURRAY: And they don't know.

DR. COX: And they don't know.

Because most of the patients that come to me as a physician don't know. It is my duty as a physician, if I know, to act on that. All right? So this is an ethical dilemma.

Now, it has recently come up in the context of genetics research--we heard it from Bartha Knopper and it was a big symposium at the American Society of Human Genetics meetings--if you have information, genetic information, from your patient, what is your obligation to tell their family members? In this country, it has been very different from what the answer is in Europe. Okay?

Now, what was the conclusion at the American Society of Human Genetics meeting about this? The conclusion was that--and it was a compromise position--that still you would respect your individual patient but there would be designated examples that would be exceptions of which you would be justified of going and telling the family member, examples that would put them at extreme risk. All right?

Thank you.

So the issue then is again coming up with exceptions, coming up with the examples of when it would be possible to breach the firewall. And it is the same situation of giving people information back. It is not that you have it open all the time.

Carol brings up a good point. Some people want to know, some people don't want to know. So you have to deal with that situation. We are not going to have a million of these different examples, but this is one of them. And just to deal with it.

Not that we are going to be able to fix it--I don't think we are going to be able to have a single rule that is going to fix it--but we have to open the possibility of going back because otherwise it doesn't, you know, pass the red-face(?) test. There is enough people that want to know and there are enough people that don't want to know that we have to have options for it.

DR. MURRAY: The queue is forming. Bernie, Trish, Larry.

DR. LO: Yes. I think this is a really important topic for us to think about, and I think we have some tough issues to think through.

One, I think we need to do a good job of elucidating what the conflicting ethical responsibilities

and principles are because what is most bothersome to me is the reason we built the firewall in the first place was really to further scientific research and make it more feasible by not putting too much burden on researchers to get detailed specific consent.

There are a lot of other competing--

DR. MURRAY: I would very much-- My first thought was to protect the privacy of the people whose tissues are being used. That would have been mine. But you don't think so?

DR. LO: Well, I may be more cynical. I hang around with researchers too much.

I mean certainly if you hear some of the professional societies, their biggest concern is they won't be able to do research that they think really benefits humanity and science in the long term. But, I mean, privacy of the individual is on that side, but then the right of some individuals to know, and the duty to protect, you know, give them information that may make it a benefit clinically.

That needs to be laid out because I think scientists and the public are very confused about those issues and don't realize that there are really pretty fundamental conflicts.

Secondly, if we look to other situations--this goes back to Steve's point--this is not unprecedented. You know, HIV again gives you a lot of examples.

The procedures for how you go back, under what circumstances, how do you bring in the private physician as opposed to the researcher cold-calling the patient directly, are things that we should all think about. There are better and worse ways of doing this kind of re-contacting.

And then there are sort of different kinds of re-contacting. Trish, I think, was talking about clinically relevant information that an individual subject may or may not want to know, but should we at least offer them the option of finding out?

Carol brought up another example, which is sort of a twist; that if I take David Cox's model of how I am going to do 21st Century genetic research, I start with a huge prospective cohort study and, out of that, I find the 1 percent of patients of interest, and I want to go back and study them.

Now, either I can do it up-front, full consent, contact them a second time and say I would like to sit down and tell you about a study I am proposing, get your feedback, and get your consent.

Or I can do it in an anonymized way where I say I am going to not get involved like that. I am going to have the steering committee of my prospective trial add-on to the next battery of questionnaires that comes out in six months some specific questions for that 1 percent that deal more with family history and other phenotypic information.

Technically, under our boxes, you know, I have met the letter of the law.

Carol brings up an interesting point which is, you know, if the 1 percent, if I am one of those 1 percent and my neighbor isn't, and we sit down and compare our questionnaires, I say, "Hey, how come they are asking me all these cancer questions and not asking you? Why? What did they find out about me?" That is, you know, it seems to me an ethically, you know, shaky situation.

And the reason we got there is that there were incentives for some researchers to opt out of a sort of true dialogue with the subjects by sort of taking the anonymized route rather than the full consent route.

And I think that, you know, we are building in some very, some incentives that are pushing us away from the ideal of research as a partnership between the scientists and the participant. And I think we just need

to be aware that that incentive is going to push some of my--

It is a lot easier for some of my colleagues to say, "I don't have to talk to the patients." Somebody else is hired to get the information, anonymize it, feed it back to me. It is a lot easier for me.

MS. BACKLAR: I think also--I said this as though I was a private citizen from a personal point of view, but I actually think there is another issue here which has been sort of touched on in terms of HIV and so forth--there are also public health issues. I just want to put that back on the table. Public health issues.

DR. MURRAY: You mean where third parties are affected by the results?

MS. BACKLAR: Where it may be necessary to give information to a group.

DR. MIIKE: My turn? I don't think you can have a practical policy with all those exceptions and all those individual decisions.

The way I would deal with your situation, Trish, is to say here is your informed consent form, in the beginning. And you say, "Can you assure me that if some research is done on my tissue and it is beneficial I will get it back; I will get that information?" My answer

is no. Then your choice is to either sign that or not sign it.

MS. BACKLAR: But we are talking about tissue that may have been taken without consent. That was the whole point Carol brought up.

DR. MIIKE: Well, but if we are talking-- Our proposed scheme is that, for prospective, you can't use it.

MS. BACKLAR: For prospective--

DR. MIIKE: You have to give a general or specific consent so, in that case, they would not be able to use it in our scheme. The way I understand our scheme being proposed.

MS. BACKLAR: I am sorry. It is very hard to hear in here. Can you--

DR. MIIKE: Well, what I am saying is that in the scheme that we are proposing--

MS. BACKLAR: Yes.

DR. MIIKE: --not already collected samples, but samples to be collected clinically or in research, you must give a consent.

MS. BACKLAR: Prospectively?

DR. MIIKE: If you don't give a consent--

DR. MURRAY: Yes.

MS. BACKLAR: Yes. I understand that.

DR. MIIKE: So what I am saying is though is that if you then say but if in the future something happens and it is beneficial to me, or if it is something significant and I want to be assured that I know about it, and can I give that assurance, then your choice is to say, "Okay, I won't sign," or you accept the consequences of that and sign the form anyway, given that knowledge.

But I don't think we can have forms and consents that vary all over the place.

One last comment is my disagreement on the tissue sample. I just suddenly realized that I was focusing on the community aspects of it and we are dealing with individual with no community, so in those instances then, then genetics is not the only issue. So I would agree with you when we are talking about individual harms and benefits without the community aspect.

DR. MURRAY: We are going to run out of time. Arturo and Carol had indicated a desire to speak. Let me just say how I would propose to play it from here on in.

To hear Arturo and Carol, and if there is anything urgent that must be said in response to them: we will have that.

To ask-- I believe we just have Mark Sobel

speaking as public testimony.

And then to use the remainder of our time to make our plans for tomorrow.

Arturo?

DR. BRITO: I just want to briefly respond to what Trish is saying. When I originally heard Trish make a comment, it made a lot of sense about of course if you take a tissue sample of mine and later on you find out there may be some information about me, of course I would want to know that.

But going along with what Larry says it seems endless; that there are so many scenarios--just looking at the table here--so many scenarios.

When we talk about anonymous, we are talking about anonymous really to the individual but not necessarily-- Well, we are also talking about the researcher, but it is a very paternalistic way of looking at it in terms of--

If you take a tissue sample of mine, unless there is a way of me having accessibility to that tissue sample in the future--me as the patient or as the person that the research has been done on--unless I have accessibility to that, then what you are doing is leaving it up to the physician/researcher to determine what is

good for me and what is not good for me.

So going back to what Larry says, it is just endless what you can do here. And I think that you really have to make the decision at the beginning whether or not you are going to agree to the research knowing that you are not going to have accessibility to that, or that no one is going to tell you of any problems with that.

I see Trish shaking her head, but unless-- I am not sure there is a simplified manner of doing this. It just gets so complex.

DR. MURRAY: Carol?

DR. GREIDER: I think part of the misunderstanding here is that, in some cases, we are talking about tissue samples that are already collected and, in other cases, we are talking about prospective collection of samples, which is part of the reason that Zeke laid out this nice grid, which now has two rows and multiple columns.

And so what I would find very helpful--we have had a lot of discussion about this--it would be very nice to have, you know, written down, so that we could look at them, what all of our recommendations are for each one of those different instances. And then we could discuss them piece by piece, rather than having misunderstandings about

whether it is prospective or retrospective and jumping back between the two.

DR. MURRAY: I think we are there actually on most points. I don't think we are there on this issue of do we ever permit breaches of the firewall.

DR. GREIDER: Absolutely. But to go back and forth and have these misunderstandings is a little bit frustrating.

DR. MURRAY: Yes. Especially--

DR. GREIDER: It would be nice to go through and discuss that issue, but on the right side of the prospective versus retrospective. And we have to discuss both of them.

And I agree that I think we have talked about all of the boxes, but I don't think that, you know, we have ever really articulated exactly what is going to happen in each of them.

DR. MURRAY: Well, maybe not, but I think we pretty much know, for each of them, what we are doing.

DR. GREIDER: But this issue between Larry and Trish--

DR. MURRAY: Not for every question.

DR. GREIDER: --I see as one being a prospective issue and the other being a retrospective

issue.

DR. MIIKE: No, no. No.

DR. MURRAY: No. I think it is--

DR. MIIKE: No. It is a question about how much she wants to be able to know in the future, when you can't tell at the time that you are giving consent what is going to happen.

And I am saying that you cannot devise a policy that will satisfy the Trish's of the world in every instance that she wants. And so you must make a choice at the beginning about either to say, "Well, then I won't participate; I don't want to participate," or "I will participate given those limitations on what is accessible to me."

I mean, I think that is the only kind of practical choice that you can make. You cannot make these very specific consent-type agreements and promises down the road that cannot be fulfilled.

DR. BRITO: Can I just-- I know you want to get on to the next thing, but when we are talking about these boxes, we are talking about the--

What I am seeing here is the anonymous tissue and then the identifiable tissue. That is identifiable to the researcher. Unless there is a way to make it

identifiable to the individual involved in the research, then I would agree then there is a way. But I am not sure if that is logistical. Maybe David or somebody who does a lot of research can answer that.

But would it, you know, maybe at the beginning, you could make some access code or something so people can identify their tissue in the future. I don't know. But I think unless you can do something like that, I agree with Larry.

DR. MURRAY: Steve?

MR. HOLTZMAN: The sense in which we have been talking about anonymized is research conducted in an anonymous fashion by which the paradigm would be that there is a sample, it is associated with an individual, it is held by someone who is distinct from the researcher, the researcher knows it by a number--all right?--but the researcher doesn't have the ability to go and identify the individual.

So the issue boils down to here, in your consent process--we will come back to the retrospective ones in a moment; let us deal with the prospective--whether or not you are going to include in that consent either a statement that says there will be findings made, some of them might be relevant to your future health

status, but you will not know about these. You will not be informed.

Or rather you will create a process, such as for example Yale has a process which Levine describes in the notes from the national breast cancer stuff, the Arena Primer stuff or, as you see in what Primer struggled with, should we have something where it can be a very generic statement.

If a finding is made in the study which is potentially beneficial to you, or could be actionable by your physician, your physician will be informed. Whatever. A mechanism would be set up. You don't have to be specific. All right? Just say it is basically that you leave the avenue open to go back if there is benefit.

The downside on it? The downside is if the major concern is privacy--the major concern is discrimination based on privacy--have you put the, have you opened up, by opening up the possibility of going back, have you created more problem than you have solved?

What we clearly heard I think from the fora, the public fora, is people think, "Hey, I can learn something that, if it benefits me, I should know about it." It just seems like the human thing to do. All right?

DR. MIIKE: That is not the situation I am talking about. I am talking about the research down the road after that one.

MS. BACKLAR: Oh.

MR. HOLTZMAN: But if you think about-- In the case of the sample collected in the clinical context where there is no specific contemplated research, all of the research is down the road.

The national breast cancer example is specifically oriented to stuff collected in the clinic.

DR. MIIKE: Oh, no. That is my point. When you know what you are going to be doing in that research, of course you can make promises like that. But it is the subsequent uses that I am talking about.

MR. HOLTZMAN: Well, that is what I am talking--

DR. MIIKE: And those are the kinds of things that she wants to--

MR. HOLTZMAN: Which is what I am talking about, too, Larry.

DR. MURRAY: Yes.

MR. HOLTZMAN: I am talking about that.

DR. MURRAY: And I think that is what showed up in the Primer Conference and what actually showed up in

at least the mini-hearing that I attended.

MR. HOLTZMAN: Right. Because it is also the case it is in that future research and/or things that come up in the research that you find out which may not be the object of your study even to begin with. Okay?

DR. MURRAY: Trish has something to say on this--

MS. BACKLAR: It is just a--

DR. MURRAY: --and this may well be something we are going to have to talk about again tomorrow.

MS. BACKLAR: It is just a request. I would like to have in front of us--maybe tomorrow if it is not too difficult--Bartha Knopper's remarks that David alluded to because I remember them but rather vaguely.

DR. COX: Just very quickly, Tom?

DR. MURRAY: Yes.

DR. COX: I think you articulated beautifully. You responded to Carol's challenge and articulated beautifully where, with respect to the boxes, this point was. We were in prospective. And also the options. We either have a process for going back or we don't.

And a final point that you made that I would like to really emphasize is a motivation for doing this is different public interest groups and different IRB groups

really think that this is something that is worthy of consideration, even though it is difficult, Arturo, as you point out. It is very difficult.

You know, it is hard to imagine how you can do it comprehensively, but is it worthwhile thinking of mechanisms? Okay? Is there any mechanism that is possible? Well, these other groups are thinking of such mechanisms. In some ways, we should at least consider potential mechanisms.

DR. MURRAY: An historical note. I was on the committee of the ASHG(?) that wrote, with Bartha, this paper that she spoke from.

And basically the paper, as I recall, simply adopts the sort of points to consider of the previous President's Commission article about when, if ever, do you breach confidentiality under certain circumstances.

And I don't remember the exact list, but there are three or four things--some of you here may have them memorized--that might fit quite well in a kind of recommendation that we would make in these circumstances, so they would be the rare occasion when the firewall might be breached for the patients, for the tissue contributor's benefit.

But we don't have any more time to talk about

that today, I am sorry to say.

I think we owe-- I apologize to Mark Sobel for putting his testimony off but, Mark, may I ask you please to take the microphone? And if you don't mind one more time indulging us with the ritual of identifying yourself and your institution.

STATEMENTS BY THE PUBLIC

DR. MARK SOBEL

MOLECULAR PATHOLOGY DIVISION

NATIONAL CANCER INSTITUTE

DR. SOBEL: I am Mark Sobel of the Molecular Pathology Division of the National Cancer Institute.

I would like to address three issues based on the discussion that you have had this afternoon.

One is an issue that Dr. Shapiro brought up that I don't think you have really followed up on, and that is who decides what box things go into? And I would like to provide to you an example that occurs at NIH for intramural scientists, which is that the intramural scientist does not have the right to decide what box it goes into.

There is a triage system, which we call the Office of Human Subject Research, which I think exists in many institutions as well. Before it goes to the IRB,

there is the determination, by somebody--a third party--that it is or is not exempt from further review. And I think the commission might want to consider such a recommendation to be included as part of this mechanism.

The second issue is related to the discussion this afternoon about genetic information, whether or not it is separate or distinct from medical information. And I would urge you to include the general feeling that, in this report, that genetic information is just like other medical information. And there are many examples of non-genetic research that are potentially stigmatizing or harmful and vice-versa.

However, it has been pointed out that there are some specific cases which are potentially more dangerous or harmful to subjects. And I would urge you to consider looking at the National Cancer Institute's guidelines for giving out certificates of confidentiality which outlines a series of specific types of research that might be potentially harmful and that might lead toward the granting of a certificate of confidentiality.

And they have a nice booklet now that they have just come out with that summarizes the rationale that could be used, and you could refer to that.

Finally, I would like to address the most

contentious issue for this afternoon, which is the firewall concept.

The pathology consensus group did state that there might be situations in which researchers might come up with information that they feel would be potentially advantageous to the research subject, however the research was performed in an anonymous manner. And it was always a possibility that the firewall might be breached.

At the time we proposed an IRB or some clinical review board be in place to consider such specific requests but, once that request was made, that would really involve, if it was future research as Dr. Cox pointed out for a subset of patients, that would really involve a new proposal requiring specific informed consent for getting new information or new samples from people.

And in the case of patients or research subjects that would like information that they think might be clinically relevant to them, I would urge you to limit that scenario because, as most researchers know, most research in the early stages is quite speculative and we really don't know what the penetrance and what the real meaning of it is.

And so I think we need to educate the public and you need to include in your report information for the

public that stresses that, in the long term, research does people good, but in the short run there are very often misunderstandings and misinterpretation of research data.

And that is the whole point of peer review and letting things incubate in the literature until there is a consensus so that there should be rare situations when it would be necessary to go back to the research subject with clinically relevant information.

The reason that CLEA(?) was passed was to protect the public from the misuse of research data that was performed in non-certified tests or with tests that really do not meet the requirements of test validity and test utility.

DR. MURRAY: Thank you, Mark.

I can't help but note that we probably have helped to create that problem. How many times have we read an article that reports some very, very basic science discovery that says it might lead to a cure for cancer? Right? And subjects read that and they don't see all the steps in between. So we have to shoulder some of the responsibility for that particular misperception on the public's part.

CLOSING REMARKS

THOMAS MURRAY, Ph.D.

DR. MURRAY: We have a few minutes left. We have to decide what we are going to do tomorrow in our roughly two and a half hours that belongs to actually us.

I think we want to-- Let me just tell you some of the things I think we ought to do, and then I am looking for guidance as to how we should, who should sort of take the lead to present the various components.

We should explain how it is that we came up with this notion of research conducted in an anonymous manner and how that differs from the prior idea of "anonymized samples."

Are you with me on that?

DR. SHAPIRO: I think that is a really critical issue for the entire commission to understand so I hope whoever does it-- I hope you will--

DR. MURRAY: Do we have a volunteer who wants to explain that idea?

(No response.)

DR. MURRAY: I mean the option is, if we don't have a volunteer, is either I appoint somebody to do it, or I do it myself. I guess it depends on how generous or self-flagellatory I am feeling at that moment.

As you know, our fellow commissioners are fairly bright folks who are not inclined to take things on

faith, so be prepared to defend any position that you are representing us on. Because that is one thing I think we absolutely need to do. We need to present the boxes.

DR. COX: I nominate you for that one, Tom, because I think you would do a great job.

DR. MURRAY: Oh, thanks a lot, David. Okay.

We need to do the boxes and explain. I think we could do it historically--in so how we started out with so many--but that is not really the best way. Let us just talk about the ones we have and why we feel they make sense, and capture the significant, some dimensions at least of the problem.

And Zeke is not here.

DR. HANNA: He will be here tomorrow.

DR. MURRAY: He will be here tomorrow. Eric is willing to talk to him this evening. Is that right, Eric?

DR. MESLIN: Yes.

DR. MURRAY: I think my inclination would be to ask Zeke to conduct that part of the presentation. How do you feel about that?

DR. MESLIN: And just as a point of clarification, that part would be his corrected original form that you didn't get today that he regretted he was

unable to provide, plus the amended boxology--the reducing the three rows to two--so that the full commission would see what had originally been discussed and what had been agreed to.

Zeke actually wasn't here when you agreed to that, but I will, with your advice and consent, encourage him to be pleased to present that, having not been here for the presentation.

DR. MURRAY: I am going to suggest we not call it a "boxology." It has a--

DR. SHAPIRO: People have been using matrices for years and we are the first ones, as far as I know--Maybe Kathi or somebody came up with that.

DR. MURRAY: Let us call it a matrix. I mean, boxology has a faintly theological and even derogatory tone--

(Laughter.)

DR. MURRAY: No. I mean, some people might think of it as derogatory and I don't want to get into that. It is a matrix. That is all it is.

We think we should talk about the community consultation idea. That is a key idea.

Now, the Human Subjects group has been talking about this as well, I take it, so it won't come as--is

that true?--it won't come as a complete shock to them. But I would be very grateful if Bernie would take a few minutes and just lay out some of our thoughts about that.

Is that-- How does that strike you?

I think the firewall issue-- The concept of a firewall, a one-way wall, will come up as Zeke talks about his matrix. The issue we were just trying to resolve, I think not fully successfully within the past half hour, is a substantial one.

I don't see any-- I don't see it as a bad thing if we simply lay out that we are having this conversation about when, if ever, or should we create an impenetrable firewall, or should we permit certain rare exceptions? If we couldn't just in fact put that before the full commission and ask for their input as well.

Because I don't think there is anything-- Not only is there nothing wrong with that, there is actually some advantage both in terms of they may have some ideas that we haven't thought of, and also it will involve them in a constructive way in helping to shape the report. So I would be in favor of doing that.

Is that suitable?

Are there other central elements--features-- that we must specifically address tomorrow morning?

DR. SHAPIRO: Tom, it is not a direct answer to that important question, but in terms of the firewall, when it should be penetrable, if ever, and so on--that whole set of issues--I think it would be helpful if one could spend some time understanding whether being unable to penetrate it would put you in an ethically indefensible position.

Quite aside from the examples that have been given here, it seems that we need to understand whether, if you took the extreme position, which I am not suggesting for the moment, but it would really be helpful to understand if you could define an ethically indefensible position that would lead you.

So that is really an assignment for some future moment when we could discuss this.

As I look--and perhaps this is part of what you anticipate as Zeke's presentation tomorrow--that is, the current matrix of possibilities shows that consent is not required for some, under certain circumstances for the retrospective samples; that is, the far-left row.

And I just want-- I think it is important the commission understand that. I am not-- That seems fine to me just myself, but it is just I think quite important that Zeke outline that, draw their attention to that

issue.

DR. MURRAY: Yes.

As we talk about this, sort of the pro and con of whether to ever breach the firewall, lots of people were very articulate about it. Two in particular I thought were Trish and Larry.

Would the two of you be willing to just sort of present, you know, without necessarily, you know, feeling cemented into the position, to presenting the view, A, I mean, of Trish's view that it might be desirable to permit it and Larry's view, from a policy standpoint.

Would the two of you be willing to sort of set the debate off for us on that? Okay.

I think we have the four essential elements. There is a fifth which we could integrate into Zeke's presentation and that is the idea, which I thought was a very good one, about how--going forward from here, in the future--how we would deal with the issue of consent.

And, as I understand it, the way we would deal with it is to, you know, have a consent. We are going to talk about the features, et cetera, without giving a model form, but we are going to say that, in terms of the process, it seemed to us to make sense to have a consent

more or less at the time of tissue donation.

And if someone chooses not to consent then and there, obviously they are out.

But for people who do consent then and there, we also send them, or give them, to be sent back within a couple of weeks, if they change their mind and they want to remove their tissue from the research pool, they are going to be permitted to do that.

So it is you must have a positive consent, plus people get a second opportunity to change their mind. Is that-- Is that how you recollect our discussion about that? We should at least mention that.

Carol?

DR. GREIDER: In this presentation that you are saying that Zeke is going to make about the matrix, are we going to have him go through and discuss what we have suggested as how we would fill in that matrix?

DR. MURRAY: Yes.

DR. GREIDER: And in doing so discuss with the full commission what we believe each one of those ought to--

DR. MURRAY: I think we have to.

DR. GREIDER: Sorry.

DR. MURRAY: Yes. Without spending two hours

on each of the boxes, yes, I think we have to.

DR. GREIDER: Right. Because in the past, when Zeke has presented that, first we focused on should this be the matrix that we are discussing? Do we have the right categories?

DR. MURRAY: Yes.

DR. GREIDER: And I would certainly prefer if he says, "These are the categories that we have come up with. These are our reasons." But then go through with the commission and say what the different suggestions would be in each one of those.

DR. MURRAY: Yes. I mean, I think you are right. We have made the jump from are these the right categories to these are the categories we are working with now and here is how we plan to fill--

(Simultaneous discussion.)

DR. GREIDER: So first maybe just discuss that?

DR. MURRAY: Yes. It is important-- I mean, I am sensitive to the fact that people in the audience may not have had copies of the matrix to look at when we are talking about 1a, 2b, you know, et cetera. Let us make sure we have a transparency, or some way to show the people what we are talking about, and not just the

commissioners.

MS. BACKLAR: So have them make 2 and 3, 1? I mean, not-- No, no, no. I don't want to confuse things. One is 1. Two and three are--

(Laughter.)

(Simultaneous discussion.)

MS. BACKLAR: Yes?

DR. GREIDER: One and two and that is it.

MS. BACKLAR: Good. Okay.

DR. GREIDER: Right?

DR. MURRAY: There is individual and there is community, right?

DR. GREIDER: Right.

DR. SHAPIRO: Carol, if this weren't a Genetic Subcommittee, we could call the boxes "cells."

DR. GREIDER: Ahhh. Okay.

DR. MURRAY: All right. Anything else urgent that we need to do today?

(No response.)

DR. MURRAY: No.

ADJOURNMENT

THOMAS MURRAY, Ph.D.

DR. MURRAY: Thank you. It has been a very constructive-- Did you want to say something, Eric.

DR. MESLIN: Just very quickly--

DR. MURRAY: Before he adds that, let me just thank you all. It has been a very constructive day.

Eric?

DR. MESLIN: For those who were following the agenda and noticed the item which was "Future Commission Research Activities," we did not get to that today. That is only because of timing.

This is an issue that the full commission will be discussing tomorrow and it is the result of the informal discussions that a few commissioners have had at the request of the chairman to start strategizing about the future reports that the commission will take on.

So you may want to think about that a little bit this evening, but there will be time--a considerable amount of time--tomorrow afternoon devoted to that subject that will be led in the discussion by Eric Cassell.

DR. SHAPIRO: Finally, let me thank Tom for his Christmas cookies. Thank you very much.

DR. MURRAY: That is okay. See you tomorrow morning.

(Whereupon, at 5:03 p.m., the meeting adjourned, to reconvene as the meeting of the National Bioethics Advisory Commission the next day, Wednesday,

January 7, 1998, at 8:00 a.m.)