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DR. SHAPIRO: When I mentioned two o'clock I rather thought that was hopelessly optimistic but we're only a few minutes after that. But I appreciate people returning so expeditiously. We have really the entire afternoon, whatever that turns out to mean in our minds, to deal with the tissue samples report, and you received a lot of material of various kinds in the book, which I'm sure will be referred to as we go through this. We in fact looked at some of that material yesterday afternoon. The comparisons that the staff put out between current regulations and our quasi-tentative position, vis-a-vis the positions of other professional societies that have an interest in this matter. And that's generated some discussion, which I think probably foretold, at least in some small way, some of the discussion that's going to take place here this afternoon. So, with that, let me turn it over to Tom, and ask Tom to lead us through the discussion of this issue. We'll try to break maybe around 2:30 or something of that nature and then just continue as.... Excuse me—3:30. I apologize. Tom?

DR. MURRAY: Thank you. Thank you very much, Harold. The scheme insofar as we have one for this afternoon is that I'm going to present for a few minutes some of the considerations that I'd like you to think about. Carol has very graciously offered to present the most recent version of the matrix. Have to try to articulate what it would mean and how it would function for us. She also will help me, I think, on some of the earlier presentation—I invite others to join in.

Let me set a framework. The goal as I've assumed of our work on this subject is to come up with a workable, defensible policy. So I've just scribbled four virtues of a policy that I hope we can embody in this. One is it should be simple; that is, it should be no complicated than necessary than absolutely necessary. If we reach a point where keeping or collapsing a distinction is about a 50/50 call, to me that says we vote in favor of collapsing it. We keep the policy as simple as we can without doing an injustice. Second, it should be transparent. That is, it should be obvious to a reader, both as to what is required under the policy and as to the policy's rationale. Third, it should show respect for donors. And we'll talk more about what it would mean to be respectful for the donors of tissue. And fourth, it should facilitate research; that is, it should not impose unnecessary or unjustifiable barriers to valuable scientific research.

And I just want to—I put them up there because I want to keep them in mind. There will be a tendency to multiply difficulties. And focus on subtleties. I just don't want us to lose sight of what we're in the end after. Please disagree with me if you think those are the wrong virtues. I'm sure there's—others could improve on that.

Second, I want to indicate where I think we agree on points that are significant. When I say "we," I certainly mean—I believe I mean the Subcommittee. I don't know if I speak for the full Commission on all of these or not. But let me try to mention five points where I think we agree.

Number 1: We agree that there is an important distinction to be made between samples that have been collected prior to whenever the report is effective and samples to be collected in the future, and that our policy should reflect that distinction. If anybody obviously disagrees with that, I think it's probably good if you indicate so right now.

Second: For previously collected samples, I believe we agreed to collapse the distinction between samples collected in the course of patient care and samples collected in the course of research. We have—we give reasons why that—we think that distinction probably can be collapsed. We have not agreed to collapse the distinction for samples to be collected in the future. That remains an open item for discussion.

Third: I believe we agree that research is important and that human biological materials, including those collected in the past—in some cases with minimal or even no concern—are a very valuable resource for science.

Fourth: I believe that respectful treatment of donors is essential, and that will mean several things. It will mean in one instance no use in research when the donor has objected. And the objection can be a general objection; that is like the donor says, "I don't want my tissues used in research, period." Or it might be a specific objection. A second meaning of respectful treatment will be that we should protect donors of tissue against discrimination, against intrusions on privacy or other harms to that individual. We can do that in a number of ways, two of them being by assuring within reason that the sample tissues, which they donated, are not identifiable; or, alternatively, we could obtain meaningful consent.

MS. CHARO: By collapsing the distinction between samples collected in the course of clinical treatment vs. research?

DR. MURRAY: We're talking about samples historically collected.

MS. CHARO: I think we lose the opportunity to use the notion that the samples were ever donated, because those collected in a clinical context often are not donated in any sense; they are surgical waste. People did not necessarily donate anything. Even though, even in a research context we say, well, tissue was being collected and donated, although it may be for several different purposes, none of which are currently on the table. You could use the word "donate," by collapsing the earlier distinction, I find myself particularly nervous now when you talk about people having donated things in the context of your respectful treatment of their donation wishes. In many cases, there are no donations and therefore wish.

DR. MURRAY: Carol.

DR. GREIDER: We talked about the issue of clinical care versus research and how they were obtained, and I feel that the consensus that we came to is because there were such a variety of circumstances in both cases and there was no way to really ascertain in many cases what kind of consent was given, that we should assume the thinnest possible or no consent for both cases and give the highest standard of protection that we would give whatever we decide that is. So, because we were going to have the same—we don't really see them necessarily as the same issue, but the way that we would treat them are going to end up being the same because we don't have any control over them.

MS. CHARO: Right. I have no problem with the collapsing of the distinction if the focus will then shift to what information, if any, exists about their choices concerning the use of the tissue. It's simply that I think at this point we can no longer use the phrase "donation" with all the connotation it brings to mind...of people having anticipated use and agreeing to it in any capacity.

DR. GREIDER: And we didn't have that in mind. We had in mind that we could not....

NEW SPEAKER: That's my term. It's probably a better term, Alta, because much of it, probably the great bulk of it was donated in some form, even if it was done minimally—I mean, for decades at least that I'm aware of, people have been given the option of agreeing or not agreeing to have their tissue used for research or education. And, I think it's appropriate to call those folks donors. It's, I think, beyond question that some tissue is collected probably more recently than we'd like to think—certainly in the distant past—without even that sort of minimal request. And it's not precisely correct to call such people donors.

MR. CAPRON: I thought your focus group showed that most people were not aware that this had happened to them.

DR. MURRAY: That's correct.

MR. CAPRON: So, again, I'm with Alta. Why don't we just describe the fact that the tissue is possessed by the pathologist and not used tissue that they donated. I mean, just totally avoid that phrase where we have good reason to think....

DR. MURRAY: It's the thinnest—it's the thinnest sense of having to donate.... I think something is to be gained by—by referring to the sources of tissue as donors rather than merely in some sort of neutral fashion or sources but that's not the central point. I don't want to fight over it. Jim.

DR. CHILDRESS: When you ascribe to the person who did not give consent at any point for the use. As a donor, then you are actually gaining our respectability for the obtaining of that tissue that does not hold, so there are gains and losses, and as long as it's a matter to be sorted out and if the Committee agrees, I think that we're on the right track.

MR. HOLTZMAN: Maybe the way to express your thought, Tom, is that we believe that sources of tissue going forward ought to be though of as donors and be treated respectfully? With respect to the XTAN collections, we can't make the

assumptions that they were donors and that therefore we may treat—we won't make the assumption they were donors with full-blooded intentions and then we'll have to come up with the framework but on a go-forward basis.

DR. MURRAY: I don't have a problem with that. I'm sorry, actually, that I used the word "donors" in that context if it created a problem. Because it isn't at the heart of what I wanted to say. I think we do agree about the collapsing of the distinction for previously collected samples.

Okay, the fifth point of major agreement, I believe, is that even when individuals are not—even when the tissues, biological HBMs—human biological—materials—are used in a nonidentifiable matter, I think we've acknowledged that at times the interest of communities are implicated and ought to be considered. Those are....

DR. SHAPIRO: In this case, nonidentifiable refers to individuals as opposed to groups of individuals.

DR. MURRAY: That's correct. That's correct. So information that goes forward, samples that go forward with all individual identifiers per se taken off, which could be race, ethnicity, sex, whatever. Okay, we have some big issues yet to be decided. I do want to try to offer some distinctions here. Again, if I cause you grief, speak—I'm sure you will speak up, actually. I'm completely confident. And I have to accept some of the responsibility for this. There were two different families of distinctions that were being used and not always—the families were not always carefully themselves distinguished from one another.

The first is tissue that would be used in an unidentifiable manner—in research—versus the tissue as it exists in its (forgive the metaphor) virginal state in some tissue collection somewhere, which may well have identifiers attached to it. So, the thesis—the difference here is between tissue collection, which is held in a pathology laboratory or in an institute or the National Institutes of Health where there *is* identifier attached. An investigator requests samples of those tissues and certain clinical or demographic information about them. That's all. No specific identifying information. So, we want to focus on—in a sense what the researcher has. That's the first distinction.

The second--and that one I believe that the Subcommittee, at least, felt that that was a significant distinction and a useful one.

The second family of distinctions—here's where I think we tripped up last time—is between—these are among tissues that are used in what we've called an unidentifiable or nonidentifiable manner, adopting Alta's terminology. There are several

different possibilities here. First of all, it might be that this tissue nowhere exists in an identifiable form, that the original tissue bank is nothing—all you have is the tissue and little bits of info, not enough to figure out who they're from. The second possibility is what the researcher gets in the researcher's hands has been sufficiently stripped of potentially uniquely identifying information to satisfy a standard of reasonableness, that is—and that there is no retained coding scheme linking back to the samples. So, there are two conditions here, right? Number 1.... What goes to the researcher is, number 1, bits of tissue and perhaps *some* information. Again, ethnicity, whatever. Not sufficient information to be, given the context—this is very contextual—given the context from where these came from. Very important. And IRBs will have to be sensitive to that. Cannot go back and say—I can figure out who this came from because I know what bank it's from.

MR. HOLTZMAN: Twenty-two-year-old black woman's the only one that....

DR. MURRAY: Right. Right. You know, a Denver Broncos fan in Cleveland. [GROUP LAUGHTER] Immediate give-away. There's probably not even one of those....

MR. CAPRON: That is a differential diagnosis.

DR. MURRAY: Right. And the second condition is—in this group I want to talk about right there's no coding scheme—numeric, alphanumeric, whatever—that would link the tissues the researchers received with what's held in the bank.

MR. CAPRON: No code at all. It doesn't exist.

DR. MURRAY: Can't get back.

MR. CAPRON: So that's nonidentifiable.

DR. MURRAY: They're identifiable. It's unidentify....

MR. CAPRON: Those are two categories of unidentifiable.

DR. MURRAY: Right. And—and the third one is the same as B; that is, it went forward with—not—with some information but not enough to identify. But, somewhere somebody's got a coding list.

MR. CAPRON: Well, that is to say the sample has a code number on it, and the lab has a code.

DR. MURRAY: Perhaps it's been mailed to a third country. So that—so that recovery of identification, reestablishing identity is at least a possibility. And I think—I didn't sufficiently make clear how I was thinking about the two families of distinction. Now, there's like a possibility of D and E. Well, that's okay—they're not important. I think we should make—the question we have to face is A and B—remember, A is nowhere is there identity; B is with what the researcher has there's no way to get identity back. It's only in C where identity might be recoverable, okay? Do we want to distinguish between A and B on the one hand and C, or we do we think A, B, and C ought to be treated as the same? And I think what I'm hearing from some of us is that A and B are the same, technically; but C is different.

MR. CAPRON: A is where the sample comes from a repository; it doesn't have personal identification with the samples, just epidemiology—they just have a whole lot of tissue.

MS. CHARO: I'm calling it unidentifiable because there is no code link....

MR. CAPRON: No, no. Anonymous samples.

DR. MURRAY: Nobody's got it, not even back....

MR. CAPRON: B... B—That information is there, but when it is sent to the researcher, it is not coded.

MS. CHARO: It's coded at the tissue bank but the code is stripped before it's sent to the researcher?

MR. CAPRON: In the repository it says "John Jones" next to the sample. "Eighteen-year-old white male, blah-blah-blah," and they say send me all your 18-year-old white males who have leukemia and they send a whole lot of samples, and they don't send any bit—and they say, "You can put any numbers you want on the samples for your study; we're not putting any numbers on them--they're just—here—here's a bunch of sample." So, if you turn around to us and say we want to get back to John Jones and tell you something we found or we want you to have John Jones to tell you something about himself beyond what you know now, it can't be done.

MS. CHARO: Okay. C is the one that has....

MR. CAPRON: A coding, so you could have...either way across the code barrier information could pass....

DR. MURRAY: Potentially.

MR. CAPRON: For scientific reasons.

DR. MURRAY: Alta, this is a very crucial point. It was well worth having it explained more than once. Zeke?

DR. EMANUEL: I just wanted to—there's a second possibility. Sorry. I want to go to the middle possibility. Because as Alex explained it, there's no clinical information that goes, but there are ways of dividing such coding schemes where clinical information could travel but you couldn't walk backwards. If you'll remember the woman from the Heart, Lung, and Blood Institute—whose name I have forgotten—explained that they do it by having three coding arrangements and destroying the middle one so that you have a name to a number, a number to a number, and than a number to another number and you take ut the first number to a number and you can't walk backward. You simply can't. That still permits you to have a sample with clinical information but no way to identify back to the person. That I would take or I have always understood was in the second category. And I think it's important that we come to that agreement because my suggestion is that's the best in the majority of the cases.

MR. CAPRON: It's a refinement, another description for how to get to the point, where the repository and its identifying codes or names is not linked with anything the researcher has.

DR. MURRAY: And yet if I understand you correctly, Zeke, if future information came in under that scheme, it could actually be passed on forward—is that right?

DR. EMANUEL: On this scheme—the scheme she identified—it couldn't be passed on. On other schemes where you actually don't destroy it but have certain locks and keys that only go one way, certain encryption technologies, you could have a continuous update. I think these are important things to be clear about. It's not C, because...the researcher can't go back even if you can feed in one direction.

DR. COX: I'd like to make a point here. To me, anybody can go back. It's possible to go back, right? And I'd like to leave us a very important point. We're talking about these different classes. Either no one can go back or someone can go back.

DR. MURRAY: No disagreement, David. Do I hear a disagreement from anyone?

DR. COX: Then the distinction is if someone can go back, the question is whether....

DR. MURRAY: It's reestablishable. Identity is reestablishable. And I think I prefer using a term like that because it's a little fresher. I think it's a little bit more precise. Alta?

MS. CHARO: ... In this middle group in which the researcher could not send information back to the tissue bank in a form that allows the tissue bank then to immediately send the information further back down the line. The researcher has no code by which to alert the tissue bank to which sample has which thing, right?

DR. MURRAY: Yes, I believe that's correct. The researcher cannot... There is still the following kind of scenario. I don't know if it's realistic so I don't know whether or not we should be worried about it in terms of its characterization. The tissue bank does have the names and addresses. They're asked to send all the samples for women in their 30s, 40s, and 50s who had any breast cancer. There are frequencies of things that we expect to discover, some of which are of dubious but possible clinical significance for people in terms of prophylactic treatment. They could communicate that to the tissue bank and say you now have an opportunity to go and send letters to every person whose tissue was in that sample, because you know who they are, and ask them if they would like to have their tissue specially tested for individualization of this kind of information.

So, to that extent, it offers up opportunities for going back to people that can't exist when the tissue in the tissue bank itself is not at all linked to an identifiable human being, where these options about walk-back simply are not present. What I don't know is how likely it is that this kind of two-step process could become of concern to people. And that, to me, is part of how I would want to consider this middle group.

DR. MIIKE: This is Larry. Can I say something?

DR. SHAPIRO: Yes. Go ahead, Larry.

DR. MIIKE: I think what she is describing as the second one would take it out of the class of anonymized and you would have to go back and get informed consent if we're going to be dealing with a new research study where you want to get more specific information or identifiables of the people who have donated the tissues. I

think we're mixing the two categories already in that example.

MR. CAPRON: I thought what Alta was trying to achieve was to point out the difference between A and B. In B, at that point you're no longer saying research, you're saying you may wish to go to a clinical lab, not a research lab, because your tissues were among X hundred that were sampled and found to have some subgroup of that. We're not saying you were one of the people, we don't know who had it, but there is enough of an indication, this is a preventable disease that your cells indicate you may be exposed to. That's a whole separate —

DR. MIIKE: It's again Larry. I'm looking at that example as more like, to put it unkindly, first, there's a fishing expedition where you don't really care about identifiables, and then you find something that's a good hypothesis where you really need to know more precisely who the donors of the tissues samples were, but then that takes you into another realm. It's a different experiment altogether.

MR. CAPRON: Yes. Yes.

DR. SHAPIRO: David?

DR. COX: And so, Larry, I agree. So let's just go into that other realm for a second, we're going there, so that we've done the fishing expedition. Now we're the researchers who have material that receives no codes whatsoever, and we go back to the bank and we say out of these thousand people that we looked at, we'd really like to study these hundred. And the bank says we can't help you because we don't know who those hundred are because we didn't give you any codes. And so it's not possible for the researcher, either for research purposes to go back to those hundred people, or, if they happen to find something in one of those hundred people that says that person was going to die and they could basically prevent it, they couldn't go back and say who that person was.

MR. CAPRON: That's right. They would have to go to the IRB and say are you willing to allow us to send notices to all thousand of these women if they're still alive — and tell them where the ball is in play here, that there's a 1 in 10 risk of being —

DR. COX: And the reason for that is because there was no codes. On the other hand, if there were codes, it would be possible to go back and identify individuals.

MS. CHARO: But please notice that the thing that happens here is that if there is at any level a link between an identifiable human being and the tissue at the repository, it opens up these kinds of possibilities like going back to all thousand women

and saying we'd like to test you to find out which were the hundred that tested positive on our test. If the tissue bank repository has no links to identifiable human beings, the tissue exists only with demographic information and medical records as they existed at the time the tissue arrived, then this never comes up.

And that's one of the reasons why I've wanted very much to keep these things separate. It may turn out in the end that the rules you adopt are nearly identical for the two situations. But there may still be a few special circumstances that you'd want to be able to isolate and focus on.

MR. HOLTZMAN: So then what you're imagining, for example, is Beth Israel Hospital has a thousand samples, it just has those samples with phenotypic information but no idea anywhere who they are, so suppose now we do this study with those thousand samples and we conclude whatever it is we concluded, which we would have had we been able to say you really ought to contact all thousand. We can't do that.

MS. CHARO: Yes.

MR. HOLTZMAN: What is the difference between that and then of a newspaper article that says this study was conducted on samples from a thousand people who came from Beth Israel Hospital over the last X years? Is it a lot different? I mean, in one sense, you're positing —

MS. CHARO: Wait. Wait. Back up because I didn't follow the details of your facts.

MR. CAPRON: Rather than getting a letter from Beth Israel, you pick up the New York Times and it says —

MS. CHARO: Well, in fact, this has been one of the reasons why there's been some critique about science coverage in the newspapers, that it's serving as an information conduit. People do get alarmed, they do start going in for retests of various sorts. It is not necessarily something we'd want to mimic even if that is something we can't control.

MR. CAPRON: But what response does one have to that? One response, which I sort of thought was the direction that David was going a moment ago, is when the researcher comes in with that study design, you say to him don't use that design because you're not going to be — the construct that you're looking for here is going to be the kind of information that you would have an interest in conveying to patients so you can find out more about them. So you ought to use a design which allows that

walk-back of the information. Once you have it, deliver it to the actual individuals for whom you found on your research level — and let's always be clear, these are research lab research results, they're not clinical results yet. And the IRB would say yours is a bad design, go out and redesign it. Then there was someone else on the IRB who says, "Wait a second, that's going to require our allowing without consent research to go forward on identifiable tissues, coded identifiable tissues." And that has another set of problems. That's the dilemma as to which design is better. But both of them are theoretically possible.

DR. SHAPIRO: Zeke?

DR. EMANUEL: I would just urge people to think about, instead of parsing distinction upon distinction for the sake of understanding distinctions, let's remember, and I don't want to speak any more as a Commissioner, but the goal is the ethical rules for the use of the tissue. And the distinction in your parsimony way is valuable only if it means we're going to treat them differently. So I think when we make a distinction, let's suggest how they might be treated differently or lead to different rules for safeguards. Because if they're not going to lead to different rules for safeguards, then the distinction, while it may be conceptual, isn't material from the ethical standpoint.

DR. SHAPIRO: Alta?

MS. CHARO: Well, I think actually the difference in the rules already exists, although I know Steve does not believe this. I think that the most obvious, reasonable, and commonplace interpretation of the existing regulations at 45 CFR state that any research that involves tissue for whose use consent could be obtained, and where the use does not represent minimal risk, you have to get the consent. And in light of all of the concerns about the privacy of this information and its possible implications for things like your insurability, notions of minimal risk become difficult to comprehend. But it is very much an arguable nonminimal risk.

DR. MURRAY: I got confused. If somebody —

MS. CHARO: Let me just finish the sentence and I'll give you a very concrete example, okay? You get information about mutations that may possibly predispose people to some kind of disorder in the future. They work as contractors for the NBAC staff and, therefore, have to pay for their own health insurance on an individually purchased plan rather than buying in through the Federal group. Therefore, they're screened, right?

DR. MURRAY: Right.

MS. CHARO: You want to go back to people and say do you want more information. It's not even we necessarily have information to give you, it's do yo even want to have more information. And at that point, you begin to get people in this kind of loop where they have trouble answering questions in the future about knowledge of their own conditions, which can affect their insurability. So whether or not you're still under the threshold of minimal risk becomes complex. And if you're not and it's at all possible to get back to people, you need to get the consent.

DR. MURRAY: If I understand you correctly, that could conceivably arise but only in the case, in the sort of third group, where some possibility of reestablishing identity exists. Is that correct?

MR. CAPRON: No. Alta is saying if the repository that has the information has names and you could go through this step of saying you gave us a hundred samples, we found that ten of them have this late onset lethal disease that's preventable, we think it's important that they know, and the person gets a letter in the mail saying your tissues were looked at along with others, the researchers don't know which ones they found but ten of you out of the hundred have this condition, do you want to come in and be further tested by these people who have just developed this new test as part of their ongoing research study. P.S.—Once you have that information, you'll never be able to answer the question on the insurance —

MS. CHARO: Worse. P.S. You now know that you have a 1 in 10 chance of having this. My point simply is that the rules that exist may well have trumped some of these questions of whether or not the distinctions do run with different treatment of the situation and the tissue sources.

DR. SHAPIRO: Excuse me, we have several people in line. I agree with Tom that we ought to at least be establishing some discipline in the speaking list. Do you want me to keep it, or do you want to?

DR. MURRAY: Go ahead, you keep it.

DR. SHAPIRO: Okay. Steve, then Carol.

MR. HOLTZMAN: Since you think we're disagreeing, we're not disagreeing on what is minimal risk. It's very clear that the psychosocial harms, risk of insurability, et cetera, et cetera are clearly established as something which rises above the potential for minimal risk in certain kinds of studies. The issue is the sense of

identifiability that's required of the current rule, okay? And coming to Tom's distinction, you're reading, that is the point you're pushing here is that in other terminology unless the sample is anonymous—full-stop, anonymous—"ain't nobody knows" that this hunk of tissue belongs to this person, that in itself means it requires consent. And that's how you read the reg from what I can tell. And that's how Melissa interprets the reg under A.

Melissa's interpretation of B is what Tom has been calling C; namely, the notion that it's — no, let's hang with this, it is important — that is there's a code. In between is what has been called somewhat ambiguously by others "anonymized," where that sometimes means people that came in and that came in with John Jones' name attached but it was irrevocably stripped away, and sometimes, and this is how Susan Old meant it in NHLBI or whatever it is, is that no, somewhere it still exists as John Jones is the sample but it was anonymized with respect to when it was handed to Alex's study so that there's no way of knowing.

Now, with respect to how things are being practiced today, in the overwhelming number of cases of samples out there they do not exist as anonymous samples. They exist in pathology labs where there is a place in which this is John Jones.' So that's the state of most of the samples. The state of most of the research studies that are taking place under what is believed to be the exemption is with respect to these studies and where there is no code, there is no walk-back. They are, in other people's terms, anonymized when they're handed off.

So I don't know if we agree or disagree, because it seems to me implausible to say that the correct interpretation of the reg is one in which people have been violating it day after day, year after year with the overwhelming majority of studies. Well, it's a practice. And so if one is saying this is the plain language interpretation of it, one would have to say how is it this practice has arisen in the face of it. I think that's a reasonable question.

DR. SHAPIRO: Okay. We have quite a number of people who want to speak. Carol, first.

DR. GREIDER: I just wanted to back up a little bit from going through the details of the language of 45, whichever number it is, the common rule, because I think that we're trying to do here is to lay out a framework for how to think about things. We don't necessarily have to interpret what is already out there to at least get our ideas down on paper and say this is how it should be, and then how do we enact that. Once we get that on paper, then we can figure out, okay, how does that fit with what is currently there, does it jive, does not jive. And so I don't want to get too mired

into analysis of what is already out there.

DR. SHAPIRO: David?

DR. COX: I would like to follow up in what Steve just said because I think it accurately describes the state, and also what Carol just said, which is with that accurate description of the state, then what kind of a framework do we have. I don't know what the answer to your question is, Steve. Whether people have been violating the law, whether people have been turning their eyes, averting their eyes for this, but for whatever reason that's what's been going on and it's causing lots of confusion right now. That's a fact. So, given that, that one group of people, and it's some scientists, in particular epidemiologists, and some patient groups say this is not the way to do business. That the price for protection—which is basically not being able to go back to people, not being able to link to other information, and, in fact, the reason why these things are being anonymized is for protection, there's no other reason, there's no other scientific reason, that's for sure. So it's a protection. Some people on both sides, the research side and on the patient group side, say that price of protection is too great because in order to protect, what we're giving up are some of these other things that we were talking about. And so the possibility of going back either to inform for whatever reason or for research...

So the question then becomes, are there other vehicles by which one can protect and not have to pay that kind of a price? And that would be not anonymizing, maintaining these links so that there are codes. So I would just like to make that distinction because what's been going on is exactly what Steve said. And what a lot of people are uncomfortable with, they say the way the future is going to be is that that's too high a price. I would personally agree with that because I believe that it's going to become more and more important to get more and more information.

On the other hand, that there are groups of people, and I would think that this is particularly the way it's been in the past, and this is a view that I interpret being championed by the pathology community, that nothing has really changed, nothing is really going to change, and so it's not such a high price to pay to not be able to go back. But I think we should be really clear that that's what we're talking about. And that's a first decision. If NBAC believes that it's not such a high price to pay and that we should just do this; that is, to take these things off, then it's simple.

DR. SHAPIRO: Zeke?

DR. EMANUEL: Two things. First, at least at the last hearings when the woman from the National Breast Cancer Coalition came up she did not have your

opinion, David. She had the opinion that we'd prefer the research to go ahead, it to be anonymous, and to find out in press reports and research updates. That was quite clearly her view. So the idea that people say it's too high a price to have anonymous research, at least in that group it is not the prevailing view.

DR. COX: Zeke, I did not say whether the research was anonymous or not. I said whether the links were broken so that you couldn't go back.

DR. EMANUEL: She urged to break the links and she said that was the cost they were willing to pay. That was my hearing of the testimony.

The second thing I would suggest is I don't think it's an either/or status here; I really don't think this is either/or. What we need are rules for all the possible contingencies. In some cases, you will want to do the research in a way that doesn't allow you to go back. In some cases, you will want to do the research and you might want to retain the ability to go back and identify the individual person. You don't have to make the choice now that the possibilities of research are too varied. We need to have rules for both of those contingencies at least.

DR. COX: I completely agree with that.

DR. SHAPIRO: Alta?

MR. CHARO: I would like to reiterate yesterday's plea for a set of vocabulary choices that will consist of mutually exclusive categories, each one capturing a single situation. The word anonymous has come around a few times on the table and I have a sneaking suspicion it's being used slightly differently each time. I think there's a lot of potential for people to appear to be at odds with one another when they're actually not, in part because we're not able to hear each other's meanings. That's one.

And I struggle with what those choices might be. I would suggest that unidentifiable means that there is no link of any sort any place. I take your point about coded being more complex than merely coded and need work on that category of coded with the links intact, and coded with the links broken, and then, finally, truly named and addressed. Third, I'm not sure yet whether in the case of materials that have codes that still link them to individuals that are used by researchers in ways that do not permit the researcher to go back to the tissue repository and individually report on the results of one particular sample to the repository in a way that could then in a second stage, or third, or fourth be linked back to a person. I don't know yet if that needs any kind of separate treatment. I was genuinely asking before when I said epidemiologically, you might find a situation where there are ten out of a hundred samples. But the fact that it

offers this possibility, and it's a possibility I've already encountered on my own IRB and led to months of agony about what to do about going back to people —

DR. MURRAY: Excuse me, Alta, which possibility did you encounter? Where you had links?

MS. CHARO: The possibility that researchers that had no codes attached to anything who were working with blood spots from a State lab found a particular mutation. Those blood spots were collected in the course of newborn screenings at a time when there was no genetic test for this disorder. They now wanted to have the State lab go back to the people who were the parents of the infants from whom the blood had been drawn and tell these people that a genetic test now exists for this disorder, would you like your child to be tested? It was CF, for which there was no clear benefit medically to knowing you had the disease before symptoms appear because there had never been a prophylactic treatment. But, of course, we could never research a prophylactic treatment because we never knew who was bound to get the disease. So there was an interest in getting back to the parents in some ways—not even for clinical benefit, but to think about them enrolling in research for very valuable purposes, which was presymptomatic CF prophylactic strategies. We agonized about the fact that if they did go back to the State lab, the State lab went back to the parents, sent parents into a flurry of worry about their kids, especially because of the uncertainties about the course of the illness—you all know the CF story.

That's why it occurred to me that we might want to just slow down long enough to say let's isolate this and wonder about whether or not you'd want the rules to be different. But this might have been a completely unique situation. Maybe it will never arise again, we never have to worry about that again.

DR. SHAPIRO: Tom, do you have anything else?

DR. MURRAY: I think Alta's done us a service by pointing out that the first — I sketched three groups and I was just trying to get these conceptually distinctive. I was not at that point making recommendations about how they ought to be treated. The first group, just to quickly remind, nowhere does there exist identifiable information, even in the original collection. The second group is the researcher doing this project has no way of going back and identifying the individuals. And third, the researcher doesn't have the information but somewhere there is a possibility of reestablishing identity. You might call the first—I don't know what you want to call the first one—"unidentifiable." The second, "unidentifiable, identity unreestablishable." The third one is "unidentified, identity potentially reestablishable." And the fourth, of course, is where it goes with identifiers.

Now I had thought one and two likely to be functionally the same for our policies. They may still be. But Alta I think has usefully pointed out that there might be some occasions, they might be so rare that you don't want to write the policy around them, but there might be some occasions where one and two are different. And I think that's correct.

DR. SHAPIRO: Okay. Alex, then Bernie.

MR. CAPRON: I agree with Alta that A and B are different. I agree with Steve, however, that B is covered by the present rule, which says you don't need consent in that circumstance. I think we need to address the circumstance that Alta raises. Frankly, my sense of the research that she described would lead me to say you contact the newspapers and say any child born. There's nothing unique about that sample.

But another example that might be different would be if there is some extraordinarily rare disease where you're not thinking that it's showing up in 2 percent or 5 percent of the population anyway and you can now discover that you can do it on these samples, which is what I take to be the CF thing you described, where you really think somewhere buried in these 100 people is someone with a time bomb ticking that we just happened to have found, it's really 1 in 100,000, we've got it down to 1 in 100. I think at that point it would be guidance to the IRB to say you have a new question to ask. If the question is going to come up rarely enough, then I don't think we ought to burden all of category B with the assumption that it's going to be a routine question. But we ought to make clear that it's not an automatic walk-back and then you have to balance the risks and benefits of this new step of recontacting this particular group of a hundred people and scaring them all out of their wits to save one life. That's sort of what you're talking about there. If I could just comment on Carol's point. You weren't here yesterday and we did talk a little bit about this when we were looking at the first presentation here. I believe we do have to make some reference to the existing rules even as we're thinking through. Obviously, we can as a thought process say where do we think we want to come out. But we have to frame that or temper it by saying that what we're talking about potentially are modifications in that rule. There may be extremely good reasons to modify that rule. But we ought to realize that if the reason is simply that we're standing in the way of valuable research, the rule was written with that in mind. People who drafted the rule knew that and there is something which, to me, would cause me pause if the first major act of this Commission was to say, well, for tissue research we ought to loosen up the rules a lot because this is the burgeoning age of molecular genetics and it's time to start reaping the benefits and so forth and so on. This is the framework. We are charged, on the one hand, with protecting human subjects; on the other, looking into genetics. And we have to keep the one context in mind when we're going about the other.

MR. GREIDER: Just to clarify. My only point was I don't think it's necessarily a useful thing at the outset to always be referring back to this is covered, this is not covered. What I would like to do is get a consensus about what we think the protections should be and then, once we've reached that consensus, then of course we have to go back and see is this already covered, is it not covered. But that's a relatively simple thing to do once we've decided what do we really believe the overarching principle should be that we should lay down here without worrying about the details of the current regulations. I think it just makes it more cumbersome to always be worrying about those details.

MR. CAPRON: But on the other side, it seems to me just as well to say this is the way things are now, is there a good reason to modify it.

DR. SHAPIRO: Okay. Bernie, you've waited very patiently. Thank you.

DR. LO: I think this whole exchange has been really fruitful and I think it's helped clarify things for me. I wanted to make a distinction between the various reasons we might want to sort of walk backwards in C. Some of these scenarios being talked about are really clinical scenarios, where we're going back because we have some information that some people in the study may benefit from knowing for clinical reasons. Now Alta complicated it by saying but there are also risks to going back because people might get scared, they might lose insurability and so forth.

It seems to me that is a question that is very difficult but there are a lot of precedents for that; all these HIV look-back studies when your surgeon turns out to be HIV-positive. There's a lot of experience on kind of what kind of potential information, what kind of risks, how you do it and so forth. And you usually do a combination of newspapers and direct mailings when you can.

Some of the harder questions, and I think of the more novel questions, have to do with going back to the sources of the tissue for research reasons. It seems to me there are two different ways you may want to go back and get more information. One is just going back to the tissue repository and saying, you know, when you sent us those tissues you sent just the following fields of information. We know that you have more information on these people. You don't have to go contact the person again, but, in addition to what you sent us last time, please give us whatever other phenotypic information we think is of interest. That, it seems to me, is one situation.

There's another situation that no, we really need to go back to the individual people because they have to give us more information. It is not in their record and we really have to take a more detailed family history or age of onset of the illness or

something. It seems to me once you go back and contact people, you're really inviting them to participate in another research study and then you really are now talking about individual, full, informed consent for a new study.

As I understood what Alta was saying, she was saying just the fact that I'm calling these people up and saying we'd like to invite you to be in a new study may be more than minimal risk because it may tip that person off that there is something wrong and it may be hard for them to say no, and they may be sort of sucked into a study where all of a sudden they're uninsurable. These are all very difficult dilemmas but they're different kinds of dilemmas. I think we need to kind of keep straight why we might want to go back. A lot of times we sort of mix it all up; it may help the patient, it could help the research. But the considerations aren't the same in those cases.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: The first motivation for considering the notion of a code, and that being essentially focusing on it not being identifiable to the researcher, focusing on that, yet there could be a code, was the notion that not that you would want to go back to the individual, but you would want to, for example, get further information about what happened to sample 27's progression in the disease, further epidemiological clinical information. And the issue that we never satisfied to my mind was whether it was possible to have a code which you could continue to get information that hooked up this medical record to this sample and kept coming across but couldn't be equally broken back to go back. I think we need an answer to that question. That could be very important.

What then got clouded into it was the issue of wanting to go back because you found out a result either of your study or found out something about that individual, for example, a misdiagnosis where there seemed a moral imperative, right or wrong, to go back and help. Two very, very different motivations. If, in fact, there can be a one-way code which allows new information to come across the barrier but essentially is impossible to go back to find out where it was coming from, you can satisfy I think what's the gist of your concern, Alta. You'll fail to address the people who are worried about not being able to go back to help someone, but you will simultaneously satisfy the impetus to be able to get additional epidemiological information that could enhance the study.

DR. SHAPIRO: Just to ask a point of information. If the situation is such that you want a continual supply of new information, somebody has to know the connection between the people supplying the information and the identities in those samples.

MR. HOLTZMAN: Except the follow — well, let's work this through, right. The pathologist knows that he or she is sending information about the following thousand named people to you. And each day is sending further information about the progression of their disease, right. And somehow that information is coming through to you and what you're getting is the hook of this additional piece of information goes with sample 1, this additional piece of information goes with sample 2. I'm not sure whether it's possible for an encryption scheme where it can keep hooking up to the right record but which sitting here with the record you can't go back.

DR. EMANUEL: There's a clinical and a research situation. In the research situation, this happens all the time. It happens all the time because, like the Physician's Health Study, every two years they send out more and they get more. But for the guy who is actually analyzing it, he doesn't know where these data comes from. And, again, I do think we need an encryption expert here. I have again spoken to a friend of mine who works for an encryption company and he says this is possible. This is exactly what the NSA is afraid of, is that it doesn't have the key. You can send information one-way, but the person who actually gets that information can't go backwards. There is not a collateral key.

So the pathologist would say John Jones, 1, feed that information in. The person at the other end would get 467 with that information and wouldn't know that corresponds to 1 and John Jones.

DR. SHAPIRO: I really understand that, and that seems like a straightforward, even simple scheme to accomplish where the researcher has no knowledge of who this is and can't establish any knowledge him or herself. That's very different, if I understand it. The situation is still the same that somebody could do this. And if not, why not? I don't understand.

DR. EMANUEL: I'll tell you what the difference is. Because it is the researcher who has the result and can't connect that to John Jones. The pathologist only knows, yes, John Jones was in that study, but the result of the study, right, defective gene or not defective gene, is unknown to the pathologist. That's the key element.

MR. HOLTZMAN: Yes, but this is why we need an encryption expert, okay. Because the notion that sample 1, John Jones, sample 1 in my hand, then goes through a random number generator and becomes 467 in your hands, then there is no way back. But if the next day you want more information, how can it go —

DR. GREIDER: I think that Zeke is right, that such things exist. You read about them in *Wired* magazine and computer people do these things all the time.

DR. MURRAY: One virtue of the terminology, not just the terminology, but the conceptual scheme I was proposing is if, in fact, such encryption schemes exist such that nobody can untangle it, even if you can pass some information forward but neither the possessor, the researcher doing it, nor the possessor of the tissues can ever make the linkage between the two, then those are samples that are unidentifiable and with identity not recoverable. Okay? So it fits in category B. Okay? And if such encryption schemes are the mere fantasies of computer experts, but I don't think they are, then they don't go in category B. Then they are linked and they are in category C. Do you follow me?

I don't think we need to speak about whether these encryption schemes exist or not or the precise details. I think we just need to understand what we think the implications would be if they could successfully interpose the kind of barrier that would not permit identity to be recovered no matter what. That's the key, isn't it for our purposes? Alta looks pained.

DR. SHAPIRO: Alta, then Bernie.

MS. CHARO: Yes. Because I'm still trying to make sure I know what we're talking about. I hear frequently from different people the phrase that "the researcher can't go back." But I want to make sure that they understand that if the researcher can go back with the assistance of a second, or two, or three, or four other people, if a collaborative effort can allow the researcher's result to go back to that individual, then that is an identifiable sample. It may be coded, we may be determined to never, in fact, identify the person, but it is identifiable.

So, Bernie, in your example of somebody who wants further demographic information for filling out additional fields, the only way to accomplish that is if the researcher, in fact, is able to say I want more information on this sample sitting here and can communicate to the repository which sample that is. Which implies some kind of code, which means that the repository, in turn, can go back to the person. If I got it wrong, that's just a piece of performance art for why it is that I can't follow the discussion yet.

DR. LO: I think you're right. A lot of these schemes depend on a bunch of different people who are unlikely to get together by accident or it's going to take a lot to put the people together to walk backwards. But you're right, it is possible to do. In fact, a lot of these schemes that we're talking about, these one-way schemes, it is often argued that they're also good because if you found something clinical back here in the research you could walk back. But I think you can't have it both ways.

MS. CHARO: No, no. See, I'm not trying to argue for a particular policy position here. I'm simply trying to point out if any number of people can collaborate together and make the result link to the person, there is almost certainly going to be a situation in which we are tempted to ask, "Gee, is this the time we should do that?" We may have set up any number of firewalls and the reason may turn out to be because we want to do more research or because we want to send clinical information, but some situation will arise where we're tempted to go back.

DR. EMANUEL: I agree with you. But just take the scheme where you get number 1 equals 486 by a computer generation, not by people in the room. What the researcher would have to say, he couldn't say go back to sample 486 and give me the additional field on that patient, he would have to say to the pathologist, "I need the following field, toenail size, on all of your people because I don't know which one 486 is."

MS. CHARO: Okay. That's right. And that would genuinely be different.

DR. EMANUEL: That is the scenario that I think is the right one. It's not you get five people in the room and they all compare their codes and, aha, they can figure out who it is. It is, in fact, that you can actually send it through an encryption scheme that all the person can do is say, "I need everyone," you feed it into a computer and at the other end you get the information. And no one actually can walk back. Even if you get the pathologist and the researcher in the room, the pathologist just has sample 1, the researcher has sample 486, and they don't know if 1 is 486, only the encryption scheme knows that.

If that's possible, and I think we do need an encryption expert to tell us it's possible, as I understand it, it is possible, that's what we're talking about.

MS. CHARO: But was it Carol or Tom, that was the point being made, that we really don't need to worry about whether an encryption scheme exists. It is if it is possible for human individuals—not computers, human individuals—to get back to an identifiable individual, that's one category. If it is not possible, whether it's because the links don't exist or because they've been encrypted in a fashion that's not capable of decryption, that's a second distinct situation. But up until now, what I perceived the argument to be was whether or not, for example, a coded sample where you could break the code qualified as unidentifiable under 45 CFR. And the answer is, it doesn't.

DR. MURRAY: Right. That's why I'd like to do away in our discussions with the concept of coded right now. It just means too many things.

These are the four categories that I'm trying to suggest encompass the important distinctions. Now, it's not clear to me that we need ... A and B, in particular, I think, with the possible rare exceptions, we can probably treat as if they were the same for most purposes in our policy. C is the case, we've talked about C a lot, we're reestablishing identity as possible either because codes exist to which human actors have access or because of the context you might be able to walk back. And D is identified. We all agree that if it's to be identified, consent is required. What I just want to make clear is does that capture the relevant moral categories for us. If it does, then we still need to decide how to treat the different categories and which may be combined or not.

DR. SHAPIRO: Bernie, then Steve.

DR. LO: Let me just put in one complication. I really second everyone saying we need to have an encryption expert here. I've heard talks where people say B isn't really what you're interested in. What you're interested in is unidentified with very, very, very, very small possibility which would take a conscious effort. And the difference between B and B-1, which I just talked about, is enormous to encryption experts. What they say is if you want absolute guarantees, that's one thing. If you want a system which is very, very, very, very difficult but still possible, that's a whole different technology and it's a lot simpler and so forth. So I think we need to be clear that we really want no possibility. But C—one possibility is I can just call up my buddy in pathology and say, you know, I really would like to find out who 486 was. And he says, well, I'm really not supposed to but that sounds pretty plausible and here it is. I mean, I would be extremely uncomfortable with that. But its a very easy possibility which is fraught with sort of human coercion in an institution may be morally very different than very difficult because an encryption scheme that requires getting a lot of people together in a really sort of upper level.

DR. SHAPIRO: I understand that C contains a lot of different possibilities in it. And the cost of reestablishing it would be very different in different circumstances, and it may be that we need to address that. I would leave that aside for the moment. But I think, Tom, I hope I'm not misspeaking, if you look at A and B, those are clear possibilities. Whether you desire them or don't desire them is a whole different matter. But it's clearly possible to have an A and B, and where establishing identification is impossible, literally impossible, for one reason or another, whatever the reasons are. So there are real things that go on in A and B. The same thing with C, and there's a wide variety of issues in C. And D is, I think what we all know what D is. So it seems to me that this is useful to describe it in this fashion. Alex?

MR. CAPRON: To the extent that what we're saying here is not just trying to set up categories but comment a little on them, and I know Kathi is listening to

this and is going to have to write the report, I would say that in C, I am much less worried about a CIA conspiracy view of this, that a bunch of people are going to be getting together and crack a code who shouldn't be doing it, than the situation in which someone comes forward after some research with what seems to people like a very moving case for going back when you thought you were setting it up that they weren't going to go back. Because we just have to recognize that we might want to go back because as people think is much less hard than, "We have this data that could save Mrs. Jones' life, if you would just tell us who she is." That still has all the problems that Alta talked about. So I just want us to be clear that when we're talking about something that's encrypted but is breakable it isn't just people sneaking around to break it, it's people coming forward and saying let me get back to her, I need more information about her, it's crucial, or I need to get more information to her, it's crucial.

DR. SHAPIRO: Tom?

DR. MURRAY: As I was saying when we got into this about a half an hour ago, I have this completely unobjectionable, simple categorical scheme here.... We have at least the categories clear. But I think Alta has usefully added that A and B we might treat the same but there are these cases—they might be very rare—where we might want to think about them differently. That's useful.

Bernie, I think, makes a valuable conceptual—it's not just a conceptual point, it's a practical point—that experts on information privacy will tell you it is almost always not a matter of is it private or not, it's how hard and how many resources would it require to disrupt privacy. One can imagine scenarios, fairly outrageous ones even under B, where somebody breaks into the lab, steals little snippets of tissue, and does DNA fingerprints on all those in order to make the link. One can imagine it. Not that's extremely remote, people aren't going to do it. But I think nonetheless this captures a good deal of what we wanted to do.

Now, we have some hard choices to make. I'm not going to propose specific ways to do it right now. I'm just going to say some of the options we face are, for example, these. We could — well, I can't read my own notes on number 1, so I'll go to number 2.... One thing we could do is we could place the burden of proof on an investigator, for some of the reasons that Alta laid out, that people want to be protected against discrimination. Place the burden of proof on the investigator—this is just a possibility—as to why reestablishing identity should be permitted at all. So the default presumption might be, our advice to IRBs might be that the investigator ought to put it in category B, "no reestablishment of identity possible," unless there is some good reason why you would need to have C instead. So a kind of default presumption.

And if we had C, we then might require additional safeguards, such as description of protections against unapproved reestablishment. Let's get somebody else to figure it out. Description of circumstances under which reestablishment might be sought. Procedures for review of request for reestablishment. Apparently, in your case, they went back to the IRB, which might be what we do. But we have to think about what we want there.

Now I'm just going to sort of live out two other issues different than this that I think we also need to attend to today. I hope we can get to both of them, we need to get to both of them.

The second is the whole notion of community consultation. That includes both what we would regard as the appropriate standards and procedures for determining when and what community is implicated. I don't think we're going to do this in detail, but that's the kind of thing we'll need to say in the report.

And two, we need to provide guidance for determining what constitutes adequate community consultation, which may include both identifying representatives from the community and saying something about what we think consultation actually means.

And can I say the third thing, Zeke, then I'm finished. We want Carol to go through the matrix. It might be that, we'll see how the discussion goes here, it might be that we'll get Carol to do it right after. We'll have a break earlier maybe and then have Carol pick it up when people are a little bit fresher.

The third thing is we need to also talk a bit more about consent for research with samples to be collected in the future. We've had some discussions about that. Do we wish to treat samples gathered in the course of clinical care differently from samples gathered in research for the future samples? It's a possibility. What level of consent would be required and/or permitted in these? People have talked about layered consent, general consent, specific consent. We need to spend a bit of time thinking about those.

Those are three key issues that I hope we can cover today.

DR. SHAPIRO: Thank you. Alex?

MR. CAPRON: I wanted to suggest a way of using the idea of community consent which is different than what you use and maybe we should just use a different term for it. It's the community being consulted not because the community as a

whole has a collective interest, but because you're doing the same thing you do whenever you use a surrogate decision maker. We use a surrogate decision maker when the person from whom we would otherwise get consent can't give consent, and that's usually because they're comatose or a child or mentally impaired. But in this case, we're using it because we don't have direct access to the person. And we could use the community, that is to say the generally described group from whom the samples came, representatives of that community the same way you all were using your focus groups. It would be most relevant, it seems to me, in the C situation where there's a possibility that down the road we're going to have some reason why we might want to walk back with information or ask you to walk forward with some more information. It strikes me that the analogy is not farfetched.

In case we ever start using the terminology about community consultation, I want to note that this is a different reason and a different way perhaps of consulting the community, not asking an identifiable community do you mind being put at risk because we're going to come up with information about characteristics of the people in your community, but presuming that your sample might be one of these samples, what would you feel about being put in a situation where people had information about you that they were disclosing or, conversely, you were confronted with potential information that would cause you to go through a process of facing something that you don't otherwise have to face.

DR. SHAPIRO: Okay. Tom, then Zeke, then Carol.

DR. MURRAY: Two very quick points. One is I could see that as a kind of alternative justification for why we would do community consent.

MR. CAPRON: Yes, that's why I brought it up under this heading.

DR. MURRAY: That's good. But secondly, I think it actually pertains to A, B, and C, not just C, because as long as there is a community identified.

MR. CAPRON: Okay. It became more acute to me in the situation in which it's more likely that there is a potential risk and an identifiable individual somewhere down the line. But I don't disagree at all if you think it could be used more broadly.

DR. SHAPIRO: Zeke?

DR. EMANUEL: Just a point of institutional memory here. If we actually collapse A and B up there and we have three categories, we once in our

Subcommittee, once, for many months had three categories. We got rid of three categories. The reason we have two categories on the framework is because we actually collapsed the categories. So we may be reinventing the wheel. We should think again the urge to think about the safeguard implications of making these divisions and which way they're going to fall.

The second thing I would comment on —

DR. COX: Can I ask a question about that just for point of information? So you meant that C and A and B were collapsed into one thing? When you talked about being collapsed, you meant A and B were collapsed, right?

DR. EMANUEL: No, no, no. We collapsed A, B, and C into one thing. I just wanted that to be really clear. A, B, and C collapsed into one thing.

MR. CAPRON: And we blew them back up again.

DR. EMANUEL: I have no idea where it's going to go. That's part of the advantage of deliberation. All I'm saying is we shouldn't forget that fact because it may be that we want to revisit those notes. The staff may want to revisit some of that.

As regards what Alex says, I think it's very important. In some cases, what you say is the community will be identifiable. But in most of the studies where, for example, in the framework we have individual known communities like the Physicians Health Study or the NHANES study, or in most of the studies that actually have brought us to this point there is no identifiable community. What do you go to, the physician leaders? You're going to go to the AMA and ask them about consent? Or in the NHANES, it's people from all over the country.

So, your idea works already in the category that we had thought about community consultation in the other categories as sort of surrogate, it doesn't, for individuals, if there's no community you're already looking at that has some genetic traits to it.

MR. CAPRON: No, that's the point. It isn't a community with any genetic traits where you're going to come up with any statements about that community. It's just a question of do you have some people who share enough characteristics — if you're looking at the tissues from males between the ages of 30 and 50, can you get together a group of males between 30 and 50 who have had tissues sampled at this hospital or wherever the samples are coming from and say to them, "This is the study being done, we have an IRB that generally approves it, they could use your advice as to

whether you have any thoughts about this?" It may not even be a matter that you give that group the same full rights that a surrogate has, but you're trying to take the temperature of people, saying "Does this worry you?" or does this seem — I mean, it's what you did with your focus groups that came back with a lot of people saying, no, this doesn't really bother them.

DR. EMANUEL: It's very clear — that is to say under individual, no community linkage, you are now going to have community consultation as a requirement, which we never had thought of before. That's what that suggestion amounts to. We may want to adopt that, but one should be clear what you're saying. Where there is no community linkage possible in the result, you now want to add community consultation as a surrogate? We have not held that position. We have always said we should not require that.

DR. SHAPIRO: Okay. I have some people on the list here now, and then I think we'll take a break after that. Eric, Carol, and Alta.

DR. GREIDER: No, I'll withdraw my comment.

DR. SHAPIRO: Okay. Eric?

DR. MESLIN: I have one comment and two questions to help staff organize the work that will likely come out of this discussion. The comment is to remind you that we've contracted with Professor Alan Buchanan to prepare a paper that lays some of the moral terrain out, but not in a highly theoretical and abstract way, but rather in a very concrete way that compares the interests at stake when we err on the side of protecting access to these samples, and the interests that are at stake when one encourages freer access to those samples. In the course of the paper that we've asked Alan to write, he will be considering both harms to individuals, to communities, and others in a way that I think the Commission will find helpful. We can ask Professor Buchanan to come to the March meeting and present that. His paper will likely be ready within the next week or so, and we will obviously distribute that well in advance for your benefit. That's the comment.

The two questions are I don't want to leave this notion of encryption, which has been mentioned by many. I would be anxious to hear the sense of the group as to whether (a) you would like us to identify such a person and have them simply communicate with staff the factual basis for some of these issues, and that can be fed to Kathi and she can incorporate that, or (b) do you think that this is an issue of sufficient gravity that you would like a commissioned paper and a person to come? The second question relates to IRBs. Zeke alluded to the NHANES study, and we know that there

is some discussion going on with the CDC in the use of the NHANES data. That is one of two IRBs in the country that I'm aware of, and maybe others know more, who spend some, if not all, of their time looking at genetic studies. The other is a separate IRB at the Mayo Clinic that Chris Hook chairs. Does the Commission wish to ask staff to identify information from those IRB chairs in the same way that I have suggested about encryption, or would you just like to let that pass?

MR. CAPRON: Is there a third alternative that they might actually be a useful witness?

DR. MESLIN: Yes. Really, I was collapsing the categories. You could pick A, have them give us information, or B, come to the meeting in March, which is already becoming a very full meeting.

MR. CAPRON: Or C, ignore it.

DR. SHAPIRO: Bernie?

DR. LO: My response is I think the encryption can probably be handled by staff in the paper. But I would certainly want to get input from those two IRBs just because I think the clearer idea we can have of what the issues are now and are likely to be, as people who are experiencing it can best predict an uncertain future, it's going to help our deliberations. We're grappling with theoretical categories. I think it would really help us to sort of try it out on some of the tough cases that IRBs have either faced or will face.

MR. CAPRON: Yes. Give them our schema at wherever it stands, then we say how does this fit with your experience.

DR LO: Yes. What cases have you had that are tough and does this schema help you any better than what guidance is out there.

DR. MESLIN: Just so that I'm clear. They will have that luxury anyway when we send out the report in its draft interim form. Obviously, we will direct it to as many of those kinds of individuals as possible. But would you like to have them before that point?

DR. SHAPIRO: I think so. I think that would be a good idea.

Carol, then Eric, the other Eric.

DR. GREIDER: This is just to address that specifically about these people that might come and talk to us. If they could bring a set of cases that they find illustrative of some of the issues that have been difficult for them, rather than just having us ask them questions, to bring two or three to lay before us so that we can put them in our own matrix might be useful.

... What has to be clear about the last hour and a half is that there's been a fair amount of disputation over categories. And I think you have to be careful about making it more complicated again. It was beginning to simplify clinical cases as a different situation. Bring in experience like Carol suggested—somebody's cases—but if you're going to bring in people who will tell you that—which they will—nothing can be encrypted permanently or we have a scheme, you're going to get into trouble.

DR. SHAPIRO: I think that's right. My own sense of that is there's not a big encryption issue here at all. And that there are encryption problems out there but they don't happen to relate to this by and large. And so I think we don't need to do much in that area. Let's take a break now and I think a relevant pick-up, particularly just where we are, I'd like to go to Carol as soon as we come back. Let's look at this scheme and see how it fits into what we've said so far.

BREAK: 3.29 PM

DR. GREIDER: When Tom asked me to go over the matrix that we had been discussing in the Subcommittee, first I wanted to kind of back up a little bit and ask myself a question: We've had this framework a long time, why haven't we gotten through it, and what have we learned along the way? And I came up with a couple of things which we have touched on here today but I just want to go back to them a little bit as a sort of preamble before we go back through it. And what I started thinking about is what are we really trying to do in this framework matrix that we've laid out. And it seemed to me that it was a very practical way of thinking about the kinds of recommendations that we might make about the use of human biological materials. And there's been a little bit of a conflict, and one of the reasons that we ran into some problems is that there was a conflict between sort of global conceptual frameworks and practical reduction, what are we actually do. And that we keep running into these things every time we talk about this matrix, but that we've done a lot of hard work in going through that, and so it was useful. But to think about it in the terms of a sort of practical document, at the last meeting I think it was Harold that suggested that another way of framing the issue that you could draw a different kind of a matrix, and I know that Eric Meslin has alluded to this and I've heard rumors about a three-dimensional matrix with risks, benefits, and what the third mention—I haven't actually written it out...

DR. CHILDRESS: Types of protections.

DR. GREIDER: ...types of protections being sort of a three-dimensional matrix were a different way to frame the problem. And so in thinking about that, I think that that way of framing the problem really gets at a lot of the more global issues, the sort of higher level kind of questions, whereas the matrix that we've been dealing with is dealing with more of the practical issues: What are we actually going to make recommendations for. And then I go back and ask, okay, what are we actually supposed to be doing? And from my standpoint, one of the major goals of NBAC is to sort of lay out, clarify, and articulate what the ethical issues actually are as a sort of first educational goal, to state them very clearly. And then second, to suggest practical approaches. That's my personal view.

So having come that far, then I ask myself what next. And I think that the framework that Zeke did lay out for us is very useful in the practical approach and we've gotten part of the way through it, and so I think we should continue that analysis while recognizing that we need to articulate very clearly in the actual report we're writing some of these other more global issues that have been highlighted. Okay, if there's any discussion about that, if anyone else on the Subcommittee feels any differently about what we've done, I'd be happy to hear about it. Otherwise I will go and put up an overhead. Okay, so you've seen a number of different tables, and the only change that I had to what I actually got directly from Zeke for his framework was that I added numbers so we can all refer to the ones that we have in front of us rather than just having names there. So you should have gotten this by fax, this is Table 2. And I think it's a good starting point for some of the issues that we need to discuss.

From the discussion that we just had, we can already see that there's going to have to be a certain amount of change, but let me just go through some of the what I think are the relevant features that are in the outline of this framework.

The first is that we separate out the previously collected samples from the samples collected in the future, which we just discussed and there seemed to be some agreement on. The second is that we have two categories going across these rows, an individual is implicated or a community is implicated. And I think at the last full Commission meeting we did discuss that this is just going to be one row across here. We had collapsed down the previously-collected samples. Instead of separating them into clinical care and research studies, had collapsed them into any existing samples and that was the discussion that we just had also earlier that the actual recommendations that you might put into these boxes probably wouldn't be any different if they were separated into these two different categories.

This chart that I'm showing you is somewhat different from one that went out in the original briefing book that was sent around in that it does have in the samples to be collected in the future, clinical care and research studies separated out. And just very briefly, the one that I'm talking about that you may have seen is this, where this is collapsed down. From my recollection in the Genetics Subcommittee, we had not reached complete agreement. There was a lot of discussion about whether or not we should keep these separate or collapse them. And so I think that's probably the starting point that we should revisit here, is whether or not we should keep this. So I'll put this one up now for the rest of our discussion so that we can talk about what we're actually going to recommend in the different boxes. And then we can revisit this issue about whether we collapse these down again.

Just let me get to one more thing. So my interpretation of what we just discussed over here with the A, B, C, and D would be that each one of these boxes would have a line or two lines going through it because as we discuss this, as it says here, these are previously collected samples and this is how they're going to be used, in an individually unidentifiable manner. We're changing the word anonymous to unidentifiable. But as we just said, there are more categories than just that and so one of the discussions that we should have here is how to bifurcate these and whether or not these are two separate issues.

What, to my mind, we didn't really ever get around to doing in the Genetics Subcommittee was ever articulating the reason we put in here 1A, 1B, 1C, 1D is so that we can write down in the report we think that in case 1A these should be the recommendations; in case 1B these should be the recommendations, etc., etc. Now, Zeke had given us some proposals about what he thought we should think about and those went out, again, as recommendations. But my memory is that those were just proposals and we'd never actually hashed through that in our Subcommittee. And so all of those are revisitable.

I think that's all I have to say about the actual framework. Maybe I'll just leave this up here and then we can have a bit of a discussion about it. I know that Steve had something to say.

MR. HOLTZMAN: Okay. And just very simply, our nomenclature up there to be used in an individually-anonymous manner encompassed what is sitting up here as A, B, and C. We did discuss it, maybe we didn't discuss it thoroughly enough, maybe we really do need to discuss it. But as we work through what would be the practical policy implication of how you would handle A, B, and C, what we found was they all came together; hence, we ended up putting them into this bucket of to be used in an individually-anonymous manner. So I think that's one point. And certainly we should

be discussing that again if people are uncomfortable with it or go through the logic, that's one point.

The second point is among the handouts, there's Table 5, and again I just want to call attention to this. In Table 5 using this one said what we thought was the current policy, okay, and by current right on existing samples. Table 5 in what was faxed to everyone. All right. And so what you will see is that it was at least the interpretation which has been called into question whether the current policy of "no IRB necessary" applies to all of A, B, and C. What I have heard is there is agreement that it applies to A. I think maybe there's agreement that it applies to B, but not agreement that it applies to C.

So again, this is not arguing, this is just making sure we all know exactly what has been...what's implied in what's been handed out and to identify where we need more discussion.

MS. CHARO: Point of clarification...

DR. SHAPIRO: Alta....

MS. CHARO: Yes, yes, yes, I know. Just as a matter of clarification, could you just help me understand what you mean by no community linkage versus community?

DR. GREIDER: The idea was that an investigator plans a study and determines that there will be no implications of any kind of a community here, like the proportion of people that have attached earlobes versus nonattached earlobes looking for a gene for attached earlobes. We can't think of any particular community that this would have an effect on. And so the investigator has to go...one of the proposals was the first thing that happens is the investigator says, I think my proposal falls in box 1A. There's administrative IRB review to say yes, it does fall in 1A, you're correct. Or maybe the IRB would say no, there is a community implicated in that study of earlobes, and so you need to go out and do whatever is in box 2A rather than 1A.

MS. CHARO: Point of clarification two. The researcher gets what you called and administrative IRB review to check what box he should be in.

DR. GREIDER: Right.

MS. CHARO: What is an administrative IRB review?

DR. CASSELL: Well that's another issue.

DR. GREIDER: That's another issue...we haven't...somebody...the only point is it's not just the investigator that determines what box they're in. There's some sort of review to say yes, that's correct.

MS. CHARO: Okay, you weren't suggesting that that's an existing mechanism that you're...

DR. GREIDER: No, no, no. My starting point here is we're making...

MS. CHARO: I understand the words you're using.

DR. SHAPIRO: David.

DR. COX: So I'd like to make the distinction between—and we've said this a while ago but just to make it again—between how samples were used versus whether it's possible to go back and do any identification with them. So distinctions A, B, C, and D refer to the ability to go back and do any linkage with individuals. But how they're used can group any of those. You know you can't use D in that but it will be possible to group A, B, and C, and to use C without having the identifiers even though you could go back and look at them. But that doesn't mean that B and C are the same.

MR. HOLTZMAN: No, David, I think it's very important to be clear here. If you look up here, A actually refers to the sample. If it is the case that the sample is of such a nature then it must be the case that when you use it, you use it in a nonidentified manner.

DR. COX: I agree.

MR. HOLTZMAN: I think we all understand that that's a matter of logic, right?

DR. COX: Exactly.

MR. HOLTZMAN: B and C, the first two words, unidentified, refers to how it is being used.

DR. COX: I understand.

MR. HOLTZMAN: Okay, and then we are talking about after that. How

it's been made such that the in its use it is not...the individuals are not identified.

DR. COX: I completely understand, and you're correct, both B and C, the unidentified means that that's how it's being used, right?

MR. HOLTZMAN: Right.

DR. COX: But for the rest of the world, it makes a difference in terms of how it was made unidentified. Because for the rest of the world, and including the rest of the regulations, if it's been made unidentified so that there is no way for anybody to identify it, that's one thing. If it's made unidentified so somebody else can identify it, that's another thing.

MR. HOLTZMAN: That's B and C you're talking about.

DR. COX: Correct. I mean that's all that I'm saying. And in terms of all of the professional society statements and also with respect to the regulations, it makes the distinction between B and C.

MR. HOLTZMAN: Okay. And all I'm saying is implicit in us coming to the framework we came up to there is number one, we said that the distinction effectively between B and C was not salient, and second off if you look at table 5, there was a difference of opinion about what the current reg says.

DR. COX: I understand. But what I'm trying to understand is why the difference between B and C isn't salient.

MR. HOLTZMAN: Why we reached that conclusion?

DR. COX: Correct. That's what I'd like to know the answer to.

DR. EMANUEL: The only answer is when we looked at the safeguards we'd like to put in in those boxes, for A and A-prime, if you will, we came to the conclusion that in fact they would look the same for category A and B and category C. So one of the suggestions is think of the kind of protections and safeguards we put in or have available to them put in place: IRB review, individual consent, community consent. Those are the three flavors, unless you want to add some more.

MR. HOLTZMAN: I do.

DR. EMANUEL: Okay. And when we thought about those three flavors,

we had collapsed it. It could be wrong and upon reflection, or it could also be something where the subcommittee agreed and the whole Commission doesn't agree. Both are....

DR. SHAPIRO: Jim.

DR. CHILDRESS: Of course another possibility for presentation at least when we're putting this out if not now, it might be helpful to go ahead and list all of these and go ahead and list the protections we're putting in place. It doesn't matter if they overlap. If it's clear to people that we're talking about these different matters, so wouldn't that be one way to handle it?

MR. HOLTZMAN: No, one other thing some of us discussed is that it's very important to engage the categories that have been out there by the other societies, alright, and make sure that we show how we're thinking about all of those distinctions, even if we conclude with respect to policy that certain of them collapse is unimportant.

DR. EMANUEL: I just go back to the suggestion that our subcommittee chairman made was simplicity. One of the reasons was collapsing them, at least, was conceptual simplicity.

DR. CHILDRESS: But clarity in communication is another important criterion.

MR. CAPRON: It does seem to me that what this comes down to is our discussion about C, because what you are saying operationally is—although Steve has doubts about this—most all of us seem to think that under the present regulations, C is in the 1B box. And if that's the case, it gets full IRB review, full consent, and there's no community consent process yet. And if you are saying that C belongs in the 1A box, that's where the difference lies. We really aren't departing from current regulations as to A and B; we're not departing as to D; we ought to focus our discussion simply on C. And we ought to see, as David has just suggested, are there things like a surrogate consent process or full IRB discussion even if you can't get individual consent, or a presumption that a first attempt be made to go back to the people in the tissue sample and send them a letter saying we're now proposing to use your tissues in a research, or in a series of research protocols about genetic screening, do you agree to this? We, our plan now is not to have the people who do the research know about you, but the design would allow us to either come back to you and ask you to plug more information into the system for us, or conversely us to feed something back to you if we find out something that might have some clinical relevance to you. That is different than the way that you were proposing to treat A and B on today's A and B list, right? And so I'm not even convinced that as of now, besides Jim's very good reminder, that we might want to

present C differently even if we had the same rules. I'm not inclined to think that there will be the same rules. And I would specifically, if we want to get the ball rolling, I would specifically move that we not allow such research without full IRB review rather than just administrative review; that we not allow it without some form of surrogate consent; and we not allow it without a presumption in favor of an attempt to establish agreement by the subjects to participate in research. The latter does not say research could never go forward, but as we heard from the cancer people when they were here (the breast cancer group), they have done that in certain cases. And in effect applied their prospective framework to retrospective samples. We're really talking about trading off dollars, of the difficulty of doing the research, versus protection of subjects' interests. That's all we're talking about here.

DR. CASSELL: I actually understand that, and that's wonderful because I was worried about this creeping dementia that must be ...

DR. CASSELL: It's only temporary.

DR. SHAPIRO: Bernie, and then Steve, and Carol.

DR. LO: I think another way to ask that question is why are many researchers trying to argue that C ought to be considered in box 1A rather than box 1B. And a lot of it, I think, has boiled down to the it's going to be too hard to do the research or prohibitively expensive or something. I guess the ...the question is what kind of project would you design under C but not B? What would be the benefits be? And it seems to me we have to think of different kinds of studies. And I don't...how would you classify a study where right now I'm using existing samples but next year or two years down the road I want to get updated clinical followup that's going to be part of a computerized medical record, will require no contact with the patient, and at the time I could probably say well, they're existing records now so I could do it? But it's not existing now. It seems to me that kind of study is, to me, a little different, or actually significant different, than a study that says, next year I want to go back to the repository of the data and have them get a little bit more information, maybe from a doctor or something as to what kind of clinical followup. Is that the same thing? And it seems to me clearly it's going to be different if I'm actually going to contact the patient for additional information, because that's a new study it seems to me. But it's not clear to me. I mean the arguments I've hard from the advocates of putting C into 1B really stem down to if we...I'm sorry, put C in 1B it will be too difficult, all this valuable research won't get done because it's just too hard to do. And I guess I'm trying to think of what is clinically behind that and what are they really gaining by designing studies to B and C rather than in D?

DR. SHAPIRO: Steve.

MR. HOLTZMAN: No, I think I can give you an answer to that question, okay. Let me deal with something first. I'm not trying to, in terms of the interpretation of the current reg, I don't know what's right and I'm happy to defer to your folks' interpretation that C does not fall within the exemption. It does strike me that others who've been dealing with this a lot longer than I wrote this piece of paper about what is the interpretation of the current reg. And I'd be very interested in staff having finding out how most people out there are interpreting the current reg and what the coded studies are considered to be subject to the exemption or not. Okay, so that's one point. With respect to the motivation for collapsing B and C, I think it was two-fold. I think we focused on the notion of the harm, and that if the individual was not identified then there wasn't a harm. That was one sort of piece of it. The other piece of it was that it wasn't prima facie evident how under B, you could have followup information flowing through.

DR. CASSELL: You can't.

MR. HOLTZMAN: You can't. All right. Now, what Zeke is suggesting is that followup information with an appropriate encryption scheme could be flowing through. But if you start with the assumption that that's not possible, that if there's going to be subsequent information that connects this to this, that it is logically impossible for there not to be a path back, then that gives you the reason for wanting to say I'll collapse C into B provided there are sufficient safeguards. That provides the motivation.

Now if in fact there's a straightforward way in which, while not maybe not logically impossible it's physically impossible under an encryption scheme to achieve B and yet have the followon information flowing through, then the motivation for splitting them goes apart because B and C parse off into physically-impossible to really get back in here in any meaningful way versus you can get back. Okay, that was the motivation. Was that clear?

MR. CAPRON: Steve, it's clear, but you keep assuming that one particular design exhausts category C, which it doesn't. There may be people who say I don't want it to be that hard, I don't think I'm going to need to talk to these people but I might need to. And so I want to set up the encryption scheme in a way where someone can decrypt it.

DR. CASSELL: Break the code.... But I want to get permission. And when I go through the IRB I want permission to go back.

MR. HOLTZMAN: But our assumption, I think, was that's exactly when it would trip it over into the 1B.

MR. CAPRON: That would make it identified.

DR. SHAPIRO: Carol, Alta, then Zeke.

DR. GREIDER: So I agree with a lot of what had just been said. When we set up the two categories there to be used in an individually-anonymous manner and to be used such that identification is possible, a lot of that was done in the absence of this robust discussion on walking back and what does it mean to walk back and what are all the different scenarios. We now have had a lot more of that discussion and I think I'm coming around to the point where instead of having two categories there, I would propose that we have three categories there. Instead of A and B it would A, and we'll call it A-prime for now, and then B. And we'll renumber them number. So then the question is which one of these three categories?

We just had a long discussion about whether B and C can be collapsed into each other and I don't think that anybody thinks that they really can, or maybe I'm wrong. I mean I think maybe I hear a lot of people saying that they don't think it's appropriate to collapse B and C. What about collapsing A an B? And then we're left with three categories.

DR. CASSELL: From a regulation point of view?

DR. GREIDER: From how we're going to fill in the regs here and that sort of stuff. And then we would be left with three columns or rows. Three columns, rather than two. So A and B have now become one. We've done something.

MR. CAPRON: Well, let me just say about that. It seems to be that there's...when you start off with A, I guess the idea is that you simply have a "gamish" of samples. And while you may have a little bit of data about each one of them, you don't have any identification of the individuals at all. Whereas in B, the ... you have that identification and you're going to strip it before you pass it on. And the question is is the possibility of the fact that you don't strip it well enough a way of distinguishing A or B? I'm not trying to be difficult, I'm just saying we're dealing with human error and human...

DR. SHAPIRO: It seems to me if you don't strip it well enough, you're in C.... Or D, depending on how badly you've botched it, right?

MR. CAPRON: And the question, Harold, is in that situation, if we're dealing with a combination of the abilities of the researchers and the source of the data and the IRB to make sure that the design actually belongs in 1A rather than 1A-prime as Carol's now talking where we put C for the moment, or I'm not sure where C is. Anyway, so I'm saying, yes, I think I'm basically...but I'd like to do it with kind of an asterisk saying it is important to note that when this is done from a sample source that has identifiers, care must be taken that they have truly...I mean someone may say, well, I'll just use initials, I mean that strips the identification.

MR. SHAPIRO: Right. I agree. It's important to know what you've got and not what you wish you had or something. All right, let's go to Alta, Zeke, and then Bernie. And I have a proposal on this matrix here, but let's....

MS. CHARO: Number one, in answer to Steve's repeated question of how is it possible that everybody in the world is misunderstanding this interpretation except for Alex and Alta, it's entirely possible that Alex and Alta are the only people who are right. And here's how I'm going to show you. I've been involved in two OPRR investigations. And in both cases, so out of this very small sample size we have a 100% positive rate. The PIs confused the concept of unidentifiable to them because there was a code that hid the name and address and personal identities with the notion, "unidentifiable" because nobody could actually get investigations approved for other purposes. This confusion was unearthed. it gives me the impression it's a commonplace confusion. Which gives me the impression it's very easy for a lot of people out there to have also had it.

Secondly, because of the ambiguity of words like anonymous, it's possible for a lot of people to be writing using the word anonymous and reading one another's stuff as meaning one thing when it was intended to mean another. So I think it's entirely possible that only Alex and Alta and Melissa in this entire planet really do understand these regulations. And I hope I've proved to you that we are right.

MR. HOLTZMAN: No, but you said B is included. Melissa says B is not included in the current regulation.

MS. CHARO: I never said B is included in the regulation. I said C is included in the regulation, which I was calling coded samples.

MR. HOLTZMAN: I'm sorry. They're included in the exemption.

MS. CHARO: C is not included in the exemption. Anyway. Second, I would like to urge that in light of the suspicion that as a full Commission there will be a

number of people who are at this point of the opinion that the rules governing C have to be different than the rules governing B because of the variety of walk-back scenarios that we not jump the gun on C nor on the A versus B thing. I think it's very possible that A and B are going to wind up having the same rules, but the experience of having seen just a situation in which B opened up possibilities that were different than A, in which B opened up possibilities for epidemiological studies that identified...made identifiable a relatively small number of people who could be approached for the possibility of individual testing without having its own complications, and there were two or three examples so that it's not just a matter of using a newspaper notification, makes me want to take the time to thrash through. So I would simply like to ask for the time to thrash it through as an entire group.

DR. CASSELL: What's the difference between A in that regard too? Epidemiologic study with A might do the same thing.

MS. CHARO: But in A, even the tissue repository wouldn't know who the people are from whom the tissues were taken.

MR. HOLTZMAN: Newspapers are the only way, then.

DR. EMANEUL: Not true. Let me give you ... Guthrie cards are completely anonymous, right? You can nonetheless, if you know the year in which they're collected, right, you could then say every birth registered in this State in this year we're going to mail out to. So I don't think that's the case. And furthermore, if you have DNA databanks in the future, not too distant future, you'd be able to in fact do this.

MS. CHARO: We have DNA databanks in the future there won't be any concept of unidentifiable and we need to be aware of that. This is a transitional stage.

DR. SHAPIRO: Excuse me. Arturo, then Zeke and Bernie.

DR. BRITO: Alta, if you can...when you're talking about identifiable for this small group, and maybe your experience with OPRR the two investigations, are you talking about identifiable for the individuals by means of exclusion, or are you talking about identifiable of a community of individuals because they have a certain disease?

MS. CHARO: Neither. What I'm saying is that in two out of two investigations on other topics, we found that investigators who were using samples that had just codes—they got a sample and it was coded XYZ—viewed that as unidentifiable and viewed the use of those samples that something that did not require getting consent from the tissue source. Or IRB. That was incorrect. And we know it was incorrect

because we were working with OPRR on this. Another source of fairly definitive understanding of what the significance is of a coded sample, where the personal identity of the tissue source can be tracked back. But they, because they didn't know who these people were, assumed that therefore it didn't matter about getting consent. Right? And so it seemed to be a commonplace confusion.

DR. BRITO: So there was a possibility of identifying from the onset? Of going back? So is there...going back to the original...I think someone just mentioned it. Is there a possibility where you have A, you have no possibility?

MS. CHARO: Absolutely. If I went around here today...if I went into a street and I didn't even know who was passing, and I just snatched hair from every person who walked by, I would get arrested.

DR. SHAPIRO: Okay. Zeke?

DR. EMANUEL: Can I just...I'm all in favor of expanding the framework again to analyze the protections, because I do think we're not going to make any progress until we expand them, figure out what the protections are and where our disagreements are. In light of that procedural suggestion, I would make the further procedural suggestion that we actually begin with the future collected samples because there, I think, we're going to actually have a lot more agreement. Because I don't think we're going to have the same level of disagreement on this. I think the kinds of protections, the kinds of informed consent are things that we have some models for, etc. That's merely a procedural suggestion.

DR. SHAPIRO: Bernie?

DR. LO: Well if we're going to go to the future samples, I'll pass, because I was going to make a proposal with regard to seeing how it sort of fits in with 1A and 1B. And I would argue that it's different from both 1A and 1B but it's not clearly in B for some cases. But if we're going to go to the future samples to get some consensus, let's just do that.

DR. SHAPIRO: Eric, did you have something?

DR. CASSELL: I'm sitting here trying to see all of this. I'm trying to protect the human subjects and the individual persons who happen to drop a piece of meat on the floor or something like that. On A and B, they cannot be known and they cannot..they don't need protecting without another study being done in which the newspapers or whatever may be involved. That's another study required. In C, the way a

study is written, they don't need protection because a study is written in such a way that they cannot be identified or the samples have been dispensed in such a way they cannot be identified. Now they found this remarkable thing and now they want to go back. That's a separate study and they have to come back to the IRB. If anybody wants to know who those people are, they must come back to the IRB and that's a totally different thing. That, we are now in D. Whenever they want to do that they're going back to the IRB in D. D, of course, is the other thing. And I don't see...I mean with all this discussion—it must be complicated. But I really don't see why that's so complicated.

MR. CAPRON: Let me try to answer you why I think...why I think it's complicated. Because IRB and an investigator ought to know at the outset whether or not that bridge will ever be confronted, even if they haven't yet fully committed to how they'll cross it when they get there. There's a difference in saying I'm going to develop information about you and you and you. I won't know it's about you and you right away. But if the information is interesting enough, I'm going to want to get it to you or I'm going to want to find out a lot more about you.

DR. CASSELL: But they can't do that for A and B.

MR. CAPRON: But they can do it in C.

DR. CASSELL: So A and B is taken care of.

MR. CAPRON: A and B is taken care of. I'm just trying to say...

DR. CASSELL: So we have only one category.

MR. CAPRON: We have one category for A and B to me with an asterisk saying you better be damn sure you're really in B and you haven't slid over to C by mistake.

DR. CASSELL: Now you're now in the one where the person could be at risk.

MR. CAPRON: Right. And it seems to me...I suggested to you before something which is, I think, in line with what Bernie said a moment ago, I think that C isn't in 1A and isn't in 1B, it's in something in between where the protections ought to be greater than they are in A but probably don't have to be quite as great as they are in 1B, on the chart up there. And I tried to suggest to you what those would be. I said in addition to you don't have individualized consent in advance but you do go through a

process of trying to turn those retrospective samples into prospective samples. You tell people we want to do research on these samples of this type, are you agreeable to having your samples used. And the individual researcher may say, with this set of samples that's impossible. These people are too mobile; we'll never find them, or whatever. And the IRB has to make a judgment, okay, we'll waive that this time. But they have to have full review which they don't under 1A. And secondly, I would insist upon if you're going to do that having a surrogate consent group, a surrogate group for the community that participates with the researchers and so forth and figures out is this reasonable as a person looking at is who isn't a researcher but who is basically in the category with the people whose samples are going to be studied. So I'm acting as a surrogate for all these people who we can't contact, it turns out after all. That's a concrete difference. I then end up with the question, which I think Steve posed, does the example he gives in which there is a system which allows normal hospital data that's still accumulating about this person to flow through to the researcher because of a clever encryption scheme, is that C or is it B? Is it basically that the researcher...is our only concern that the researcher can't ever go to the IRB and say please, please let me get back to them, I either need more from these people that isn't flowing in automatically, or I need to tell them something, I have something very urgent to tell these people, please we'll be doing the humane thing if you let me go. You know, that's the question. And that's only ... that's possible under C. Steve was trying to say the way he's designed his hypothetical study that's not possible and therefore we should treat it like B, as I took what he said.

For all intents and purposes, that is really a B situation, even though there really is a linkage going from patient through to research. If the researcher goes in on Day 10, the record may look different for code #75417 than it looked on Day 1 because she's come back into the hospital and they've done some more routine tests on her, and oh my God, they've got more.

DR. CASSELL: Then he has to go back to the IRB.

MR. CAPRON: In Steve's hypothetical...

DR. CASSELL: No, your hypothetical, "I want to save the human race and go back and find out more...."

MR. CAPRON: Yes, yes, he has to go back... They're different enough that he should tell the IRB right up front, and the IRB ought to look at that differently than they look at something which is really in the B category or he can never go back.

DR. SHAPIRO: Let me...I want to make a couple of comments, and also remind you that we ought to avoid just talking back and forth. There's a lot of people

who want to ... participate in this conversation. As I listen to this conversation and look at that framework that's up there represented in that matrix, there is an aspect of that matrix which I think the Subcommittee felt justifiably was new and that is this issue dealing with community issues, not in the surrogate sense which you introduced which may also be very important and find a role here, but in the sense that the information coming forward had something of some relevance to that community and one needed to address that in some way. And I think that is an important issue; both of those are important must...we'll have to deal with it. However, for purposes of trying to work out our scheme, and for filling in the boxes and so to speak, my suggestion which is simply a tactical, not a big issue of principle, is that instead of putting...distinguishing between individual communities you go down those rows, that those rows should really be these here. And then we'll come back as we go through and lay over the community issues .... Instead of individual community/community, you'll have A, B, C, D. And you will have to deal in the boxes with these community linkages but you'll have to deal with them in some way. I just believe that it'll just give us a framework in which we can work out the simple problem and deal with the community issues as we go along.

DR. EMANUEL: I thought those were columns actually.

DR. GREIDER: They're just another way to do it, right, which is to split them.

DR. SHAPIRO: Correct, that's all I meant.

DR. MURRAY: But what would be in the column category then?

DR. SHAPIRO: You could use the same thing in there as you have right now and then you can decide whether to collapse them or not.

DR. MURRAY: I think if I understand what Harold was suggesting, first, let me just clarify. Do we all agree that right now this is at least A and B? Over there belongs here, is that right? And that's D, right, because identification is possible. And we may put...C may go in the middle. So Harold's suggesting this. We sort of turn the array around 90 degrees and now each row, B1 representing A, B, C, and D. That's all, right? That's what is new. No mystery here.

DR. SHAPIRO: It seemed...I mistakenly thought I was clarifying something. I withdraw that idea, clearly not correct. Were I an artist I would try and redraw that, but I can't.

DR. MIIKE: Can you move that exhibit a bit, I'm having a hard time

seeing. [LAUGHTER FOLLOWS]

DR. SHAPIRO: Alta.

MS. CHARO: First I'd like to second Zeke's suggestion that we focus on prospective, perhaps, because going along with what Alex said, I think if we had a common set of rules about prospective collection, and we then encouraged all of the large archives to try to contact people and reconsent them along the lines that we've developed for prospective collections, we would reduce the number that exists in this retrospective with no idea what these people want because they're either refusers...well, they're nonresponders. That would reduce that size and they would be refusers, and we'd know these people really don't want to be used. And that might be helpful.

But more importantly, in response to Eric's question of why this is still complicated, the experience that I've been having sitting on IRBs in the area of walk-backs is varied. But here's what I imagine happening in the future, and I'd love some guidance on this. There's going to be the discovery of more and more oncogenes of various sorts that are part of a multigenic, complicated, environmental genetic complex that lead to certain kinds of cancers. Any one mutation is unlikely to have a clear clinical significance, but neither does it have no clinical significance. In addition, various tumors are going to be identified as genetically distinct so that there will be interest in tracking the reaction of various patients to various forms of chemo, radiation, and combos, and tracking that in conjunction with the kind of tumors they have. So you'll both be looking at people's predispositions to cancer in a complex array of mutations and the forms of cancer they have in a complex array of mutations.

Any one single bit of information you develop about any single piece of tissue is likely to be interesting, intriguing, but not definitive. We're moving into a world in which most genetic information's going to be highly ambiguous, rather than the old Mendelian model of highly-penetrating, single-gene disorders where if you have it you're going to get it, this is what it's going to look like, and now deal with it. It's going to be totally different.

There are going to, therefore, be thousands of situations, Eric, where if you permit the first part of the study, which is to go ahead and look at the tissue, right, I can predict for you that you are setting yourself up for 16 visits back to the IRB for touchy, sensitive, complicated, balancing acts about whether or not this is information that justifies recontacting for further followup of those original tissue sources, or contacting these people in order to send clinical information back down. Either scenario.

And so I think it's important that we not just say oh, well, it'll be a new

study, that's no problem, because we are setting the IRBs up for a very large number of very difficult scenarios, each to be handled—and it might make more sense—at the very beginning when you can see this is a study which, by virtue of the potential for a walk-back, can open ourselves up to 16 requests, to think about it, anticipate it slightly, and because each one of those requests is going to come up in a seemingly compelling fashion. But over time you begin to recontact people multiple times with ambiguous pieces of information, and you really are running the risk of driving people completely out of their birds. And I would just like us to not put ourselves in situations where we're on kind of a runaway train in the recontact world.

So that's why I'd like to treat C as something more than just no problem because it's a new study if you want to go back to these people.

DR. CASSELL: But, can I just respond? Just briefly, it's really brief. I accept everything you say... and that's why in the protections for future sample collection, we have to make provisions for that. But that does not mean that it applies to the protections for existing samples, or the complexities that you just introduced. You can solve that problem in future samples, but you don't have to do the same kind of complexity for existing samples. And if you say, well, we may miss a scientific opportunity, that may well be the case.

DR. SHAPIRO: David.

DR. COX: Yes, I think Alta has put her hand on, or her finger or whatever it is, on something important here. Because the ... it does become a nightmare if you think about the researcher going back and saying, oh, and I forgot to ask about the big toe and I forgot to ask about Aunt Millie. One of the things that the Breast Cancer Coalition people said to us, and a word that we haven't heard mentioned once today, is standardization. And it's extremely, I believe, important if something like this is going to work. So that it's not, in my view, or it's possible but it's not something that you'd like to see happen, that researchers could go and ask for any kind of information that they'd want back. There's, in my scheme, there would be a standardized set of information that would come back, period, that's it. There could be a menu of stuff that the researchers could ask for that would come back. It wouldn't allow them to identify the person in C. It couldn't identify the person; they'd be using the information in a nonidentifiable way. And then, if they wanted to go and do a new study, that's over and above that standardized set of information, then there has to be a mechanism by which they can contact then, or list those people for other research.

Now I think it's a conflict of interest for them to contact that person, and that's why I really like the idea of the surrogate group that's not only protecting the

rights of the patients from the researchers, so the surrogate group could do that. It could also be the group, as Alex suggested, that would deal with the issue of community, because it's the community of people who the samples are, that's what we're talking about. And furthermore, that surrogate group could predict, could protect all the other players from conflicts of interest of one or another physician that had more than one role. For instance, a pathologist that was involved with the clinical care of rooting out the samples and at the same time involved with getting the samples for research: one person playing both of those roles. that's not a "for sure" conflict of interest, but it's certainly an apparent conflict of interest. So the surrogate group could be looking, protection each other for dealing with these things. And if you have one standard set of information that can come back. And it can also be longitudinal, so if you that this thing, that this piece of information will be updated each year, you're not going back. That's what's set in there.

The .. but it's a menu that the researchers can do but it's not an unlimited opportunity to go the kitchen and ask for a completely different meal. It's like a restaurant. So, and I have...if we ever get to it, some practical examples of the existing this that meet this criteria right now.

DR. SHAPIRO: Bernie, then Zeke.

DR. LO: Two points. First, in some of our comments, I'm concerned that we don't want to set out guidelines that provide rewards to people who are either sloppy, stupid, or ethically obtuse. So that I wouldn't want to say to an institution that actually has good records, is able to go back and contact patients, you've got to go mail them a postcard and get consent for their old samples, whereas if I'm running a really third-rate organization and can't contact people, we'll that's okay, I can just go ahead and use their samples.

DR. EMANUEL: So you don't want to penalize the Mayo Clinic.

DR. LO: Right. I don't want to put burdens on them that I wouldn't put on institutions that just aren't as well, sort of, set up. And similarly, I don't want to give rewards to investigators who haven't thought through the first-time around what is my research question, what am I asking, what if we're saying, well if we keep nickeling and diming the IRB: Can I do this, can I do that?

My other comment has to do with I think we need to build into the protocol for these kinds of studies on existing samples of genetic tissues some prior thought as to how the investigator proposes to handle foreseeable dilemmas regarding recontacting patients in either direction. And I think there's, again, ample precedent. Any time we do a study that, for instance, deals with psychosocial issues, our investigators

are told, or at least we teach them or try and teach them, they've got to in their design think of what happens if I identify someone who's severely depressed, who's a victim of domestic violence. How are they going to handle the confidentiality? What backup do they have in place? And so I think part of what we need people to think about when they design the study is try and anticipate what dilemmas may arise in the course of your study that may...under which you may seek to recontact patients either to give them information or to try and get more information. And tell us how you propose to deal with those situations rather than having people run back in six months, then in a year and then two years.

So I think also the way to get around your problem is to sort of start to develop almost a standard of practice as to what are the types of information that warrant going back and warning patients in this multigenetic, incomplete-penetrant sort of model, and what are the ways in which more information from patients ought to pass to the investigator in a one-way sort of walk-through without necessitating full individual consent from patients.

DR. SHAPIRO: Zeke.

DR. EMANUEL: I want to make a suggestion. I am at one with Alta on the wish to avoid this sort of constant recontacting in the scaring people for the susceptibility genes that aren't really predictive. Now I think we can take one of two approaches. It seems to me if an investigator wants to do that kind of research on stored samples, with the possibility of going back because they might find something, we should treat it as identifiable. That's what they want to do. I am all for, in some sense, ruling out category C altogether. I have always been for that, which is you don't go back. And you ... if you want to use the sample in an anonymous manner or an unidentifiable manner, you don't have the possibility of going back. It's just excluded from you. Now, what is the usual what happens if we find something that is serious. Serendipitously we find a serious...you know we're doing some controls and we have the Huntington sheet in there, we find someone. Those are always the questions. I think it's very clear for us...we need to be very clear, either way somebody is going to end up being harmed. Whether we permit C and we're going to have a violation—we should be clear about that—or we don't permit C, we exclude C, either you go and make it an identifiable study or you can never walk back, in which case we are sometimes going to find something on sample 486 which we can't go back and identify. And the only way it'll get out is when we publicize our research objectives and people have to go decide for themselves. I think that...my own view is I think that minimizes the harms. And especially the harms of this constant recontact, constant additional information that may be very unwanted separate from a full-blown study where you get to decide whether you're in or out. And as I, again, heard the Breast Cancer Coalition, that's the way they wanted to do it, too.

I will, however, put on my other hat which is when I frequently propose this idea at various institutions, people who are clinical investigators, both clinicians and researchers, get very nervous about it. And their clinician hat rises up. I think we have to recognize that and if we come out...if we rule out C, we have to decide that.

DR. SHAPIRO: Tom, then Carol.

DR. MURRAY: Zeke, my intuitions track yours very closely, and I think I was wholly in favor of ruling out C till I went to the mini-hearing. And I heard a person, at least the one I heard and apparently this is true of other hearings, they, you know, it seemed to me they wanted to leave open the possibility that they might benefit. Now they also worry about discrimination so that would favor ruling out C. But they also felt like if they're going to have their tissue used, they would like to see if there's...if they might benefit directly from that, they'd like to see that happen. So that made me rethink whether C ought to be kept alive as a possibility. That's all.

DR. EMANUEL: Benefits there turn out to be the key problem, right, because knowing that you might have a five percent increase risk of cancer, is that a benefit? And so when you pose it to them that you'll benefit, I mean who would say no to that information? The problem is that the quality of the information, as Alta I think has correctly pointed out, is going to be completely different...than what we previously or what we're used to thinking about.

DR. SHAPIRO: Carol.

DR. GREIDER: Just to get back to this issue about whether or not we delete category C and just make it not happen, to make it be actually B, if I hear what my colleagues, David Cox and Steve Holtzman are saying, that is like currently the largest category. And so we should just be aware.

DR. EMANUEL: That's the largest category? I though B, I thought B was the largest category. David tells me repeatedly that C is the largest category and so we just have to be aware...that you're shutting the door on the largest category of maybe it's not what's going on currently, but this is where are things are going in terms of genetic research. And so ...

DR. EMANUEL: David, are you saying C's the largest category because of the continuous feed of more information? Or are you saying C's the largest category because you want to go back to the individual samples?

DR. COX: Because it's the existing largest category. Pathology

departments don't have all their samples with all the identifiers stripped off of them sitting there waiting for somebody to ask for them. Samples are sitting there with peoples' names on them.

DR. GREIDER: But you said that people want to use them in a way that they can then go back and find out more information. This was what I hear you from you...

DR. COX: That's exactly what I'm saying.

DR. SHAPIRO: Bette, and then Bernie.

DR. LO: Let me make a specific proposal which I think addresses concerns I've heard David Cox and Steve Holtzman make. That's the situation of a investigator who wants to study, do DNA testing on a large sample, large number of samples, trying to find a hundred or so people who have a mutation that she will then want to study in more depth. Obviously, once she identifies those hundred people, she's going to have to go back and get specific, individual, thick, informed consent for further studies. But that first-pass study, which is taking advantage of a large number of samples and doing tests, she's really only going want to do without having to contact the individual patients for a number of reasons. I would like to suggest that under some situations, those kinds of studies ought to be permitted with full IRB approval, without individual consent, with some sort of community surrogate consultation as Alex was talking about, provided that there's some, and also that those kinds of studies be allowed to feed onto the research in a one-way direction, clinical information that's, clinical information that is gathered from the patient in the routine course of clinical care and fed into a computerized data system so that you can get follow-up information on a patient on such things as, you know, relapse and something, or clinical follow-up, not, sort of, other bits of information. Provided also that the investigator and the IRB ahead of time work out some system for dealing with contacting the patient or setting out the parameters under which they might find it permissible to contact a patient for really, really definitive clinical findings—which I agree with Zeke—will unlikely be from that research but other serendipitous findings that would really have a clear-cut dramatic impact on a patient's health.

DR. EMANUEL: Can I clarify one thing Bernie? Why, I mean, in yours, as you've just described it, why couldn't you make it look like B in the following way: I'm going to take a thousand breast cancer women, right? I'm going to get the clinical information on the thousand, I'm going to do tests for gene Y, okay? A hundred of them are going to be positive, and I'll have the clinical information on that hundred. I'm never gonna go back and contact anyone, it'll be completely anonymous. And I'll get, and I'll

get continuous feedback.... But in an encrypted manner so I can't go back.

DR. LO: I could do that, but then, but that's not the study I want to do. I want to be able to, if I identify those hundred, contact them to invite them to enroll in the next generation study, knowing I'm going to do that very carefully because of the concerns Alta raised about, you know, jeopardizing their insurability. But I would plan to go back to them once I've identified them to get full informed consent for a next-generation set of studies. So I want that possibility of reestablishing identity after the study is done, and I don't want to have to mail out postcards to a thousand people, because I really want to get those hundred. If I only got fifty of them, my study can't be done. Now I, I've sort of tried to hear from what Dave and Steve have said, that this is a strategy that is the sort of one of the strategies that is likely to be very fruitful in future genetic research. And so I think we need to look at it closely. And I'm just concerned that if we say you really can only do this if you have individual consent from everybody, you may not really do the research in the, just, your sample size isn't big enough to get the genetic variation.

DR. COX: That's correct, and that's exactly what the community is concerned about.

DR. LO: Well then, then I think we need to address that, because I've heard it from enough research whom I respect I want to be able to say let's let's just try and address that problem.

DR. SHAPIRO: Eric, then Alta.

DR. CASSELL: But, Bernie, let's suppose we're not talking about future specimens?

DR. LO: Totally different.

DR. SHAPIRO: No, no. Just for the moment, it's the same, it's future specimens. And you, should you be asking permission for the people those specimens are coming from about just the study you're describing? It may be the case that investigators will wish to recontact you, blah, blah, blah. Is that the case?

DR. LO: Absolutely.

DR. CASSELL: Fine. So when you start your research you've already declared that that's your intention, and the consent form for it since you must have that in it in the first place, right? But this material doesn't have such a consent form. And so

to solve that problem, you need permission from whom to go get that consent? You have to ultimately get it from the person, don't you? So really what you need is the ability to get back to a hundred people and get their consent for your further studies. Is that correct?

DR. LO: Absolutely.

DR. CASSELL: Right. And that, should that be, the only question I have is, I have no trouble with that. Should that be part of your original design, I will desire to go back.... In which case, you're already talking about people who are, in essence, identified. You are not interested in the nine hundred that you, right? But you are interested in the one hundred. Therefore it's a study about people who are identified to start with.

DR. LO: Right, but the question I have is knowing all that, and by being honest about it and being straightforward, can I do my first-cut study with the thousand without getting specific individual informed consent from all thousand on their stored tissue samples?

MR. HOLTZMAN: So I go, go to Harvard Community Healthcare Plan, okay? And, and I think it's important to keep our minds wide in terms of what you might be looking for, right? So what we said to them is, "Can you go through your records and identify how large a group of people you have with high HDLs?" That is, good cholesterols. We're looking for the healthy folks here because we want to figure out those genes, okay? Do we need informed consent from everyone in the plan for them to go through and look at it? Our intent is, if there are enough folks in there that we could launch a study we would then go and enroll those people in a study.

DR. COX: But there may not be enough.

MR. HOLTZMAN: But there may not be enough. Okay. But clearly, in my mind, if we're then going to go and enroll those folks, you're going to get involved. Now, on the other hand, let's take it further, right? So suppose they come back and say yes, we have *N*, and *N* is a large enough sample to do it, and it so happens we have in the fridge bloods from all of them, okay? Now. Question. Under what conditions can I do a study on those bloods without consent? And those are, they're current, they'll be sitting there. And since you're continuously getting more information about these folks because they're part of your plan and they're going in for their annuals and it's going to take us a couple of years to get to the gene, can you feed us forward—I don't want to know, I don't want to go back, but just as part of their regular health care, can you feed us forward any additional information about their HDL status, or whatever, that's

changing? So when David was saying the future of genetics, okay, and does it mean you have to go back and mail the individuals or what. You can imagine these scenarios where you don't have to talk to the individuals, you don't have to know who they are. Someone is in possession of information.

DR. COX: Do you need their names?

MR. HOLTZMAN: I don't need their names. I don't need, then, well let me, again, the question again comes back to in what we've described and I thought was the motivation was that it was unclear that you could be, be B and get the go-forward information. Okay? The clinical follow-up information. So when you say it's C, I don't know, does it need to be C or not? So, but those are some real-life cases. I also want to say we shouldn't be so focused on genetics because, in the sense of "the mutation" and "the genetic study," most of what we envisage here in terms of particularly the cancer is not going to be looking for germ 1 mutations it's going to be looking at differences in RNA profiles, transcriptional differences, and protein differences, which may not be indicative of inherited genetics.

DR. SHAPIRO: Thank you. David?

DR. COX: Although it would be really nice to make this case very simple, that it's not sort of laziness on the part of the researcher not to sort of declare that he or she, you know, has this in mind to begin with. But it really depends on what that initial sample looks like. And why this is a real problem is this is exactly the way NIH is setting all this up. They have these samples that were done with these detailed informed consents. The tiered informed consents, there's lots of samples collected that way now. And researchers want to go in and initially use those in this sort of unidentified fashion, a C-type fashion. They want to make sure it's in a C-type fashion because they don't want to go to the work of getting the informed consents for everybody to begin with. But, if it looks like a sample that's going to be worthwhile to them, then they do want to go in and do the informed consents. Some of those samples, they can go through a lot of them. Let's say that there's ten different sets of heart disease samples and that you find out it's only one of them that really has the groups that you're interested in. So, that's the one that you'll go in for the full IRB approval. Now I'm not saying that this is the way it should be. Right? I mean I'm agnostic about what we should be. I'm just saying the way that the research community is thinking about it now. Some the way Steve said, others the way I'm saying. I don't want to argue which is going to be more.

MR. HOLTZMAN: There will be both.

DR. SHAPIRO: Bernie?

DR. LO: I'd like to repeat a session I've made before. I would find it immensely helpful if we could get a chapter or mini-chapter from scientists saying, "These are the types of studies we think are going to be really fruitful in the future," just to ground us and make sure we have in mind the kinds of studies that, at least in the short to medium term are likely to be proposed and raise the dilemmas. Also, I think that for the public at large, I don't think they have any clue that these are the kinds of studies that we really have in mind. I think it would be important to add some sort of real-life description to our analytic categories to make people understand what's going on.

DR. SHAPIRO: Okay, we have a few more people on the list here. We're going to have to draw our discussion to a close this afternoon. We're obviously going to have to do some staff work here to try to take this discussion and give it a framework which seems sensible to people. We're not going to hone that down this afternoon, we just don't have time. But I have Alta, then Eric.

MS. CHARO: First, I want to say that the examples that Bernie and Steve gave are extremely sympathetic examples for why you'd want to be able to make sure you can go ahead and do the research. I'd also like to note that retaining the requirement that there be some form of consent does not necessarily preclude doing this research. For example, you might actually get the consent. Or, you can have a version of consent that is essentially an opt-out, and that handles the problem of the now missing people. It's a letter that goes, "We are planning to do this kind of stuff and if you object, please get back to us," with the presumption being that those who don't get back to you are either actively consenting or we're going to simply draft them in. Because this is in the realm of minimal risk. Right? And indeed the exemption is written to anticipate that if you reasonably can't get consent from people and it's minimal risk you really don't have to worry about consent. We're talking now about a possible change in the regulation where maybe if it's not minimal risk you'd want to debate whether or not an opt-out is appropriate. But nobody here is suggesting that we shut this research down. The question is, how much effort do you make to allow people an opportunity to be aware that they've been made into research subjects while this goes forward. And although the examples you give seem completely innocuous, the problem as I've said, is that there are unexpected things that seem to crop up. You're looking at healthy people with high HDLs and then a lab halfway across the planet in Nagano, Japan comes up with something that links high HDLs to, uh...

MR. CAPRON: Schizophrenia!

MS. CHARO: Schizophrenia.

MR. CAPRON: So we ought to put our two reports together.

MS. CHARO: That's right. [Laughter] My point simply is that if it's possible to work out a system by which we make a serious effort to notify people and get some consent or at least a lack of objection, we can go a long way towards making it easier to live with ourselves when these situations inevitably arise down the road. And we can talk about how when we do it. This is a national issue, there are 228 million samples—fine! Let NIH with its new expanded budget finance a $100 tax credit for every person who say yes on a checkoff on their IRS tax form. I mean we've got national-level endeavors we could talk about that would allow you to get out at least one blast of alert and notification or something. I mean these are nonsense ideas at a quarter to five but I'm not willing to abandon the idea that you've proven that these studies won't if we try to live up to our ideals about not roping things into, roping people into things that they didn't know about and putting them at risk of getting phone calls they didn't expect or spouses who see the letter or get the phone call saying, "I never knew you had breast cancer," or "I never knew that you were once at Harvard." Or whatever it is that the, the recontact incidentally tells other people in the household about: your past and your medical past, your social past.

DR. SHAPIRO: Talking about that very last risk of never knowing you were at Harvard, I repeat an anecdote that occurred to me that I witnessed in an elevator in New York, in the elevator. One man is saying to another "All three of my sons went to Harvard." To which some women in back said all four of her husbands had gone to Harvard. [Laughter] No consent, no anything! [Laughter] Eric?

DR. CASSELL: Well Steve, I hear your case is an excellent case, and one of the questions we would ask you is, "Do you need consent from those people to do the study as it exists now?" We can make a case that you do not, or no harm will come to those people and the data will never get connected to them, and so forth, and that's the issue. If the data cannot get connected to them and you cannot go back, cannot go back, then we don't think you need consent—the specimens have already been stored. Now the, and what I hear again and again is "Yes but angst! Because look, it will turn out that schizophrenia..." Well then that's the way it will turn out. And you can't go back. Period! You *cannot* go back. And, and if we understand that then things become easier. If, in the future, you want consents gotten that allow you to go back, that's a totally different thing. And the, and the fact that scientific progress may be slowed down doesn't move me at all. I'm not moved at *all* by that.

DR. GREIDER: Not by, not a bit?

DR. CASSELL: No. Not a bit. Not an absolute bit. Progress is only one value.

DR. LO: But Eric, how about clinical then, if it's the patient?

DR. CASSELL: Clinical benefit to the patient also! Because remember, it isn't clinical benefit to the patient—it's clinical benefit versus harm! And since you have a number of people, to *the* patient against how many harms? That's like when you say about an in ICU thing, "Well he might live, well he might live!" How many people do you keep on respirators, that one person might live? Those things have tradeoff. It's easy as long as you're concentrating on "The benefit will come—we'll be able to show that schizophrenia and HDLs are intertwined..."

DR. LO: No, no, I'm saying, no, I'm, see I think we really have to keep clear...

DR. CASSELL: And we'll get that person treated and they'll never have a break, whereas if we hadn't done this work they would have gone ahead and broke it.

DR. LO: No, Eric, I think we have to really keep clear. Wanting to contact the patient for research purposes either to get more information or to get them to, invite them to enroll in a future study versus contacting a patient because serendipitously in the course of your research you've found clinically relevant information for that individual patient. If you found it on an employment screening exam you would feel obligated to tell that patient that he has tuberculosis or...

DR. CASSELL: I know that but you're doing the same thing. You're isolating it as though it's this example. We may benefit *this* patient rather than the wider screen of *all* similar studies. All studies done with that caveat built into it. You see, if you look at that one patient, look at, at the injury. But if you realize that we're not talking about one patient—we're looking at a spectrum of studies of which that's one example. So yes, you can make a persuasive case for that one patient. But if that's the way all studies of that type are designed then remember, you're protecting an awful lot of people. And, in fact, some people do get injured when you protect a lot of people, so I'm not moved by that.

DR. MIIKE: Can I interrupt?

DR. CASSELL: Okay, Larry.

DR. MIIKE: I agree with Eric on that. We either have to fish or cut bait on some of these issues, and we can't let the individual cases sway us on the overall. The second thing is that Steve's example about wanting to go back and go back, I look at that and say "What if I was a patient?" It seems to me the fact that there's some tissue or

some blood stored is irrelevant. I would feel offended as a patient if I knew, if I didn't know and was not informed that they were continually tapping into my medical record with my never, ever knowing it. So to me, I would call that, and I, I would, I don't know how you deal with that but I certainly wouldn't want to give my consent on that.

DR. SHAPIRO: : Thank you. We'll take a couple of more comments. Then we're just going to have to break and try to...you'll have the last word in a moment. Eric, you wanted to say something?

DR. CHAPPELL: No, I'm okay.

DR. SHAPIRO: Okay. Alex?

MR. CAPRON: I actually have two questions now. One relates to the exchange earlier between Steve and David. And that was the notion of a person doing studies on a whole bunch of different samples and one of them turns out to be the one of interest. My understanding of that exchange was those were all studies being done of the "B" type. That is to say, you didn't have the linkage and you didn't get consent in advance, and so forth. Having then identified this group, you then wanted to do a "C" type. Is that a correct understanding?

DR. COX: No, that was Steve's. We mixed those. It could either have been by the "B" type, and then you have to look at the whole group. I'm particularly interested in those being of the "C" type, where you actually knew, not from the outset, but you would by looking at the group. You wouldn't have the links as a researcher. You'd have all thousand people. You would identify samples 23 and 32 and somebody else *could* have told you who those were.

MR. CAPRON: Yes. Okay, that's "C" type.

DR. COX: And there are two, clearly very different things. Because one of the things if you wanted to go back, you'd have to go back to the whole group, right, if you wanted to inform them. The other you could only just go back to those two people. So, that it would be sort of much more cost-effective from a research point of view. But, the risks, as Eric has pointed out, for those two people increase considerably, so...

MR. CAPRON: And the second is to follow up a question on what Larry just raised, because maybe everybody else saw this before, but a little while ago Steve was describing a study, and we were trying to decide whether it fit in "B" or "C" and it was the one in which there was a one-way flow of information from an ongoing patient

into a database and then the researcher was looking at it. And Larry just put his finger on something which has been my sense about it all along, which is that sense of sudden shock and a little bit horror to discover that all your stuff was flowing in, it wasn't just your doctor that was looking at it, but someone was doing research on it. Are we clear that that's referred to as a prospective study, or are we, are we trying to bundle it under retrospective? Because you start it off looking at existing data and the next time you look at that data it's been supplemented, but at that moment that you look at it, that new data is also "existing data" even though you've set it up, to allow yourself to constantly get, as it were, prospective data. The data is existing by the time it's, because "data!" But are we judging it, in other words, from the point where the research taps into it or at the point at which the researcher begins the study? Because Larry's comment makes me think what I originally thought before I sort of put it out of my mind, which is we ought to treat that as a prospective study at that point. Are we in agreement about that? Okay.

MR. CAPRON: ...you're saying "as you come in and supply new data I won't know who you are, but I will know your new data." You know, I can't treat that as a retrospective study.

DR. SHAPIRO: Rachel, did you want to say something?

MS. LEVINSON: Yes. I have ten years' experience working in a pathology lab on tissue. And I have to say that "C" is the by far the biggest category. And I couldn't call it prospective after the first cut either, necessarily. An example might be where you have a hypothesis that normal people (this is something I worked up) normal people have thyroglobulin in their retro-orbital muscle. And some people develop an autoimmune disease that causes their eyes to bulge out because they're reacting to the thyroglobulin in their, their eye muscle that's there with everybody. So I go and I get 200 samples of retro-orbital muscle and I look for thyroglobulin and I find it. So I know that these people have it. Then I want to know something about thyroid function. I go back to medical records at that point. And I didn't have the patients' names, and I didn't care about the patients' names. I got the tissue and I had numbers of the people. So there's a record in pathology that says "this is autopsy tissue from "A"...98-137. And I can go back and get from medical records from that number their record of thyroid function. It's still old, existing data in the same medical record. Then, I find something that's a little different and I want to go back again and look at, still, existing data. It's normal people, still, nothing about disease function, to try and get more details to understand how the variability would come out. Today, we would look at the genetics of it. But, it's probably the largest type of a study. The most frequent type of studies that are done. And you never need to know the names, ever. You can do it all by numbers.

MR. CAPRON: But it's still "C."

MS. LEVINSON: It's still "C." But...

MR. CAPRON: It isn't prospective, because it's all...

MS. LEVINSON: It's not prospective, it's all existing data.

MR. CAPRON: It's all, you're looking at it, just on the day that you, you start the study.

MS. LEVINSON: Exactly, you're just cutting it different ways and going back and asking questions.

MR. CAPRON: Whereas if you were having the patients at the same hospital were coming in for annual physicals and their eyes were being examined, and that data was flowing in to the data banks, that would become a prospective study.

MS. LEVINSON: That could become a prospective study.

DR. LO: The real question is do we want to get full consent from each individual for the second study but not for the first study? Because that's a big difference in how feasible that research is and how much effort. And I think it's not how you categorize it, it's what kind of protection you think is appropriate in each of those two situations.

MR. CAPRON: Yes, is my answer, where you're going to be tapping into new data, the person who's supplying may really become a subject in your research and they ought to know it. And the opportunity is there. They're coming in, they could be asked. This isn't one of these things where you start wringing your hands where you say "they're dispersed, we don't know where they are, they might be dead, they may be," right, whatever. These are people who, they only are relevant to you because they are still coming in. And, they are becoming current subjects in your study, as people, not just as tissues, they're not just tissues anymore, they are people coming in.

MS. CHARO: But you're acting as if the retrospective study wouldn't require consent, and if you link medical records, as I understand the rules, you need to get consent even if they're existing medical records. If I have a piece of stored tissue here and a medical record in a different room, and I want to do research that involves linking information between the tissue and the record, or if I've got two different records—I've got a dental record on avenue "A" and an opthalmological record on avenue "C" and I want to link them. My understanding, under the current rules, is that if, if consent is possible I need to get it. It's one of the most commonly, if I've got it

right—I think do—because it's one of the most commonly misunderstood things, along with confidentiality versus unidentifiable, that we've run across in our PIs. Because it seems so totally harmless. Because they don't care about the patient's name. And they're shocked, *shocked,* to find out that they need to get consent. And yet, I've, this has come up endless. So we don't want to have this discussion about prospective versus retrospective as if it means different rules, as far as I can tell. It's the same rule! You've got to get consent.

MR. CAPRON: And they say, "of all the IRBs in all the world, why did she walk into this one?"

DR. SHAPIRO: Okay! [Laughter] That's right. I think we ought to move to adjournment now. This obviously, it's been very helpful, but I think what it tells us is that we have to get back to this group. Tom, I'm going to turn to you in a moment. But get back, try to assimilate all this and find a structure that seems to allow us to begin building the kind of protections we want. I actually think myself that as we start articulating which protections belong in which box, however you do these boxes, that a lot of this is going to seem much more straightforward. That it'll be pretty easy in a lot of the boxes, and then there will be some very difficult boxes to decide. Just whether we need informed consent or don't, in certain... But I think it's really quite doable. Tom?

DR. MURRAY: Thanks. A first quick word of thanks to Carol for presenting the matrix and for helping me get my own thoughts clear, and David was also very helpful in that. To Harold for chairing the meeting with characteristic graciousness—I'll let Harold say the final words about staff. And Alex for acting as our host. But I have to say I'm shocked to disagree with Alta about something. Not what you last said but your comments about testing for schizophrenia in Nagano. [Laughter] I'll have to tell you right now that, you know, at the eve of the opening ceremonies for the winter Olympic Games, they're not testing for schizophrenia at the lab in Nagano, they're testing for anabolic steroids, stimulants, diuretics, and beta-blockers.

MS. CHARO: And Sudafed!

DR. SHAPIRO: Well, I've actually discover, I've discovered something about Tom—that he's really big on these athletic analogies. [Laughter] And we're going to have to investigate this, where this comes from, that enthusiasm. But, we really thank everybody today. Alex, thank you, it's great to be here in Los Angeles. It doesn't look like it's raining too hard out there right now. So, thank you all very much.

[Scattered applause]

ADJOURN 5:25 P.M.