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The meeting was convened, pursuant to notice, at 7:35 a.m., THOMAS H. MURRAY, Ph.D., Chairman, presiding.

APPEARANCES:

GENETICS SUBCOMMITTEE

THOMAS H. MURRAY, Ph.D.

MR. STEPHEN H. HOLTZMAN

MS. HENRIETTA HYATT-KNORR

CAROL WIDNEY GREIDER, Ph.D.

MS. RACHEL LEVINSON

EZEKIEL J. EMANUEL, M.D., Ph.D.

KATHI HANNA, Ph.D.

MS. BETTE O. KRAMER

LAWRENCE H. MIIKE, M.D., J.D.

DAVID R. COX, M.D., Ph.D.

ALSO PRESENT:

MS. DANA KARR
Center for Health Policy Studies

MS. PATRICIA NORRIS

ELISA EISEMAN, Ph.D.
Critical Technologies Institute
Rand

JAMES WELLS, Ph.D.

MR. SEAN SIMON

MS. SHERI ALPERT

ROBERT WEIR, Ph.D.
University of Iowa

MARK SOBEL, M.D., Ph.D.
National Cancer Institute

FRANCES PITLICK, Ph.D.
American Society for Investigative
Pathology

I N D E X

P R O C E E D I N G S

WELCOME

By Thomas Murray, Ph.D.

CHAIRMAN MURRAY: I welcome everyone to this morning's meeting of the Genetics Subcommittee. If I keep my welcome to 30 seconds we can actually be on time, because at 7:40 Elisa Eisman is going to talk about what she has learned with respect to tissue samples and sampling.

Elisa, please.

DR. EISEMAN: Oh, that's it. Okay.

CHAIRMAN MURRAY: That's it.

TISSUE SAMPLES AND SAMPLING

By Elisa Eiseman, Ph.D.

DR. EISEMAN: I passed out a very small handout. It should be on the top of your pile. Pretty much I'm just going to talk about the first page of that hand-out, but the second and third page is kind of more detailed information about what I'm going to show you on this first page.

So the version of the report you all got is still a work in progress. A lot more information has been added in the week or so since it's been passed out to you. I'm still trying to plug in numbers, and at some point I'm just going to have to call it quits and go with what we have. But I think the numbers kind of speak for themselves.

I just wanted to highlight a few things that I found while I was doing the report. The first, is I thought I would highlight the biggest institutions that have stored tissues samples. So the single institution

with the most stored tissues is the Armed Forces Institute of Pathology, and that houses both the National Pathology Repository and the Department of Defense DNA specimen repository for remains identification.

Combined, there is about -- well, the Pathology Repository has 2.5 million cases, which actually is about 92 million specimens, and the DNA specimen repository has 2 million specimens. They actually collect three specimens from each enlisted personnel.

The largest funder of tissue banks is, obviously, the NIH. Cumulatively, graduate medical education teaching institutions or academic medical centers have the largest and oldest stored tissue samples. So, if you put them all together, they have quite a large number of samples.

Now, to the table. The vast majority of tissues, as you all have already guessed, were originally collected for diagnostic or therapeutic reasons. The top three places, again, would be the AFIP Pathology Repository, pathology specimens at

pathology labs, and then the newborn screening labs. That is captured here as part of the large tissue banks. Actually, this 2.6 million and the 95 million under here, most of that comes from the Pathology Repository.

The pathology specimens represented here only represent at this point those at academic medical centers. I have not been able to yet get a number for other pathology labs, which there's probably at least 5,000, if not more, besides academic medical centers.

Then the newborn screening labs, which this number of 10 million is a very low estimate. It's based on a report that came out in 1995 from McEwen and Reilley and it's taking all their lowest numbers and their ranges and adding them up together to this 10 million. So, it's much over that because there's one place, California, that has over six million samples itself.

DR. EMANUEL: Can I ask a question?

DR. EISEMAN: Sure.

DR. EMANUEL: In your draft report, Table 4 and 5, I don't know if you remember them.

DR. EISEMAN: Uh-huh.

DR. EMANUEL: These are the anatomical, clinical. Those are buried in the 100 million?

DR. EISEMAN: Yes, they are.

DR. EMANUEL: Okay.

DR. EISEMAN: Basically, what I did for that number -- that's a good question, Zeke. When I added up all those together and took the 400 and some graduate medical institutions that had pathology programs I came out with, they were collecting about 5 million cases per year.

What I also did, was took the number that I got from talking to the pathology chairs and the length of time these samples are stored ranged anywhere from 20 years to 100 years. As I took that five million, multiplied it by 20 million, and came out with an estimate of 100 million, which is probably pretty fair. Considering that only represents about 400 medical institutions in the United States --

DR. EMANUEL: You're definitely low-balling it.

DR. EISEMAN: -- it's very low. It's very

low.

The other thing that I wanted to comment about, these cases that were collected for diagnostic or therapeutic reasons, is that they're all identified or identifiable samples, by virtue of what they were collected for.

If you add up the top three places, you come up with 112.5 million cases and 202 million specimens that were collected specifically for diagnostic and therapeutic reasons in this tally. And as you can see, if you look at the grand total that includes everything, that accounts for the vast majority of samples that are out there.

The other samples that I wanted to highlight are the blood banks and organ banks down at the bottom. The blood banks do collect quite a lot of blood samples per year--it's about 12 million--but most of those go straight back out the door for transfusion purposes. At any one time they probably have in storage 20,000 to 40,000 units of blood.

Organ banks. Again, the vast majority of them go straight back out the door for transplantation

purposes, although some are specifically used for research. A lot of the eye banks, if the eyes are not suitable for transplantation, we'll then use them for educational research purposes.

The forensic DNA banks that collect and store tissues from criminals. Probably one of the other bigger collections, which is a very low estimate here and I'll tell you why, is the longitudinal studies. That information is very hard to track down and I'm still in the process of trying to get numbers. I've tried to identify quite a few of the longitudinal studies. Only a few of them appear in the report right now, and I kind of just outlined the other ones I'm going to try to get information for.

But this number of about 26,000 is quite low because it doesn't include numbers for the Nurses' Health Study, which I just yesterday found out has over 80,000 samples alone, the Baltimore Longitudinal Study, the Health Professionals Follow-Up Study, Physicians' Health Study, Family Health Study, and multitudes of others. So a closer estimate, and again, it's probably going to be a low number, is closer to 1 million

samples in these longitudinal studies.

DR. COX: Elisa, do we have the CDC stuff?

DR. EISEMAN: That actually is included in this too, to a large degree.

DR. COX: The 263.

DR. EISEMAN: Yes.

The last --

DR. EMANUEL: From a realistic standpoint, I mean, the importance of that is that those ones are, first of all, all already collected for research.

DR. EISEMAN: For research, right.

DR. EMANUEL: And because of the extensive data collection on those people, they're most likely to be used for additional research --

DR. EISEMAN: Correct.

DR. EMANUEL: -- of all the samples here.

DR. EISEMAN: Correct. Exactly.

The last two that I wanted to point out are the sperm and embryo banks, and the umbilical cord blood banks. Again, that number that I'm showing for the sperm and embryo banks is quite low. At least on web sites and printed literature, most sperm banks

don't advertise how many samples they have, so it's a bit of a problem tracking those down.

But I am in the process of doing that. That number includes information from California Cryo Bank, which is one of the largest. They publish every month a new catalog that has 200 donors in it. So again, I did a little bit of a hand waving.

Also, the Virginia IBF Institute, Genetics and IBF Institute, does have an embryo bank that has about 23,000 embryos per year that they collect. So that's a per-year number, actually, for only two places, which is quite low, again.

Then the last thing is the umbilical cord blood banks. That number is probably pretty close to accurate. It's probably a little bit low. I've identified about half a dozen umbilical cord blood banks since I gave you guys the report, but these have only been around for about five to six years, because it's a very new technology.

So, all told, basically, for a very low estimate, which still is a lot of samples, I'm trying to differentiate between cases. A case would be me, I

go in, I have a biopsy done. That biopsy is a case, but that biopsy might be five slides and a paraffin block. Those are what I'm calling specimens. So specimens will always be more than cases.

I came out with a grand total of over 113 million, and I put two greater than signs, because it's going to be much greater than that. Probably that should have been carried through the whole bottom of the table. Number of specimens is about 220 million, so, on average, maybe two specimens per case, at least from what's been reported.

Then the thing that I think is quite interesting is that, where it was reported, and that wasn't very often, I'm still getting 16 million cases/specimens, depending on where they're being collected, per year. So not only is this a huge storage of tissues, but it's being added to significantly every year.

DR. MIIKE: Twelve of the 16 is blood.

DR. EMANUEL: Yes. But, Larry, if you look at the pathological specimens and you carry over to five, we know that there are more than five million

operations--just operations, forget biopsies--a year. I think there's 15 million or so operations a year. You assume that each one of them should result in a pathological specimen. She hasn't done any of the community hospitals in that pathological.

DR. EISEMAN: Right. I'll try to include that in the final report.

DR. MIIKE: What's your estimate of those non-academic specimens that relate to research?

DR. EMANUEL: In the past, low. In the future, who knows?

MS. KRAMER: From community hospitals?

DR. MIIKE: Yes.

MS. KRAMER: In my husband's community hospital, he happens to chair this IRB. For his monthly meetings, he comes home with two briefing books, two books that make these look like they're thin, and that's just to get through for a monthly meeting. So the number of research protocols going through that community hospital is staggering, and increasing.

DR. EMANUEL: I think the thing is, to the

extent that a lot of them are beginning to affiliate with academic health centers, they now realize that there's a value to the repository. You're going to see a change in the dynamic.

MR. HOLTZMAN: I think the question we should be asking ourselves is, we have established that there's a lot of tissue out there, which we knew, but it's useful to have data on occasion.

What do we want to draw from that fact, are the sorts of things that come to mind. We've learned--let me throw out a few things--that a lot of the discussion, I think, in the past about, what is the appropriate way to think about issues like consent, have started, perhaps naively, with the paradigm of a specimen collected under a research protocol, or is, in fact, the overwhelming majority of pathology samples. What difference does that make?

The second, is what is the quality of the annotation associated with these different kinds of samples, because it's the annotation that determines what kind of research one can do with that.

You pointed out, Larry, a lot of it is just

blood, and that's true. And if all you had was, it's blood, that it came from a person, there's not a lot of research you can do. When it's disease-specific you could do things like looking at prevalence of a certain polymorphism in a population. It would be useful for that, but that's about it. So, again, I'm going to come back. What is it we want to learn from this; what are the morals we draw?

DR. COX: Can I take a cut at that? I find this extremely useful. This is going to be pretty reductionist, so I apologize.

But, first of all, do these categories break down evenly? They're not even close to being broken down evenly. So then if they're not broken down evenly, then in the kind of context or the kind of structure, like Dr. Weir's paper, which we'll get to later today, it raises different issues for different categories of these.

So at least what I would say on this is that we don't blow off a category just because it's low amounts, but that we prioritize categories in terms of where the greatest amounts are. That doesn't make an

amount equal to the importance of ethical issues, but at least in terms of the pragmatic, practical things. It could be a very useful guide to our discussions.

Stephen, what I'm not doing is saying sort of what the substance of that is, but it's more a process. It helps guide the process. Because I am most concerned that we'll get focused into one or another of these types of tissues or types of ethical issues and not cover the whole thing. So, at least if we're going to go, let's cover the things where there's tons of samples. That may be even the easiest one to do.

DR. EMANUEL: The other thing I saw in your report -- I mean, one other way of looking at it is not just the number of samples, but in some sense, how likely is it to produce research results? Therefore, one estimate of that is, how many papers come out of it? It was only the NCI's tissue network, whatever it's called, where we had, I think, some estimate of paper generation. They said something like 2,000 over the last 10 years.

I mean, one thing is how we might weight each of these for the likelihood that they would be used,

and one estimate of that is, where do the publications come from? I think it's obvious that the longitudinal studies are going to be the highest in terms of publication, but, if we had some sense for the others, obviously we're going now from back-of-the-envelope calculations to pure guesses, in some sense, because almost no one but the NCI, probably, makes some sense of how many they publish. Maybe a few academic health centers with a pathology department, in arguing for money every year, tries to say how good they've been to everyone else. But I think that might be another helpful measure for us. Again, crude estimates.

DR. COX: I really agree. That's a very good point.

DR. EMANUEL: What's the use going to be, or likely to be, or historically has been?

MR. HOLTZMAN: But you would need to inflect that against what have been the policies for access.

DR. EMANUEL: Right. Of course.

CHAIRMAN MURRAY: This is a question along the same line, and I don't mean to put Elisa on the spot to answer this. But it would be helpful if we had a

better sense of which of these categories had been likely to be used for research or would, in fact, be usable for research in the past, and, then given Zeke's comments about how health centers are aggregating and having tissues which may not have widely been used in the past, tissue collections might now be used in the future.

What particular subcategories here would be more likely to be utilized in the future? I don't know if anyone here has any insight into that, other than the past and the future.

DR. COX: Well, Zeke just said, and this is my personal perspective, but I think in the future the longitudinal studies, depending on what the access policies are for the future, will probably have a big impact. But I think that there's no question that the pathology specimens have been the sources for the past.

DR. EMANUEL: Here's a completely anecdotal. I mean, in Boston there is now a major food fight over who is going to get primary access to HPHC, Harvard Health Care. Just because it's population based, they

have lots of good data on their electronic records. I don't know, I think it's 400,000 people. So now everybody wants to be affiliated with them suddenly, for this kind of research.

MR. HOLTZMAN: And if I could answer that less anecdotally, but it's true, because we're one of the people.

(Laughter)

MR. HOLTZMAN: I think we have to assume that more and more samples will now be used for research because people are recognizing the value of those collections in many ways. In fact, many of the collections which maybe, up until now, have been collected in a manner where they're not terribly useful, everyone is organizing themselves in new ways with new, more systematic annotation, and data collection methods so that they can be useable.

So I know that as we, my company, talked to more and more pathology centers and community health plans and whatnot, they are very much looking for guidance as to, what are we allowed to do here, how should we do this in a manner that's ethical? So it's

even more pressing than maybe a year ago.

MS. KRAMER: So, Steve, perhaps we have to make the assumption that all of these specimens are going to be valuable going forward from here, and take that into consideration when we draft our guidelines.

MR. HOLTZMAN: I think you do.

CHAIRMAN MURRAY: That's a good summary, Bette.

MS. KRAMER: Right. Forget what has been and just go froward from there.

CHAIRMAN MURRAY: The notion ought to be that they may be usable.

MS. KRAMER: Right.

MR. HOLTZMAN: And again, as one casts one's mind broader in terms of the nature of the research, even the most thinly annotated sample can have a use, for example -- prevalence of a polymorphism in a population.

DR. COX: Having said that, though, Bette, the chance that they'll be used equally is extremely unlikely and that the sources and concerns with them vary tremendously in terms of different issues with

each source. So this isn't news to us, because we already did this grid. But I've heard similar to that.

DR. MIIKE: Well, do we have readily available to us, or potentially, representative samples of the kinds of samples that are across these categories? Because clearly, to me, the longitudinal study should have a much more specific -- consent than any others of these.

MR. HOLTZMAN: We do know their range, right? I mean, newborn screens. They range from no consent because they're mandated by law, ranging up through the most full-blooded consent, and throw in there also the Army samples where one could ask, what is the nature of the consent in that context. It runs the gamut.

DR. EMANUEL: Even the longitudinal studies -- I mean, if you look at something like the Nurses' Health Study, the Physicians' Health Study, a lot of the tests they're doing now were not predicted when they took the samples. Right? I mean, part of the value of the samples is that they're 10 or 15 years old. The fact is, at that time they didn't have --

DR. MIIKE: That's going to be the case for

today, too.

DR. EMANUEL: Right. Exactly. So it's not going to be very specific consent. What it's going to say is -- I mean, I presume we could get a consent from the Physicians' Health Study, the Nurses' Health Study. I haven't taken a look at it. But you know that when they collected it, there weren't all these genetic tests, for risk of thromboembolism or cancer, whatever. So they couldn't have specified that.

DR. MIIKE: I wasn't looking for specificity, I was just sort of looking for, in the minds of the people who were then collecting it, whether they had an idea of what they were going to be doing down the road. It seems to me that, just given this range and what you've just said, I don't see how we can possibly come up with a uniform policy across all of these uses.

DR. EMANUEL: No, I know there isn't. But that's what we're searching for. I don't think we're going to get it.

CHAIRMAN MURRAY: Elisa?

DR. EISEMAN: I think Steve makes a good point. With some of the older longitudinal studies

that have been ongoing for quite a long time, the consent might not have covered as many tests as are possible.

But at least for, like, the Women's Health Study that is ongoing now, they're very conscious of a low of issues. So they actually, when I talked to them, read me a large part of the consent and were very cognizant of sensitivities like genetic testing, and did allow people to opt out of having their samples being used for genetic testing.

So some of the newer longitudinal studies might have better, or more informed, consents. But the participants might be more informed of the types of tests that might be done on their samples versus people who are enrolled in studies that are much older studies.

But if you'd like some of these places--I know the Women's Health initiative I could get the consent from, and some of these other places--I'd be happy to try to attach that as an appendix if that would be helpful.

CHAIRMAN MURRAY: I think that would be

enormously helpful. Also, it would be helpful to get some samples, probably without identifying the institution from which they came, of some typical consents for clinical specimens.

DR. MIIKE: We can ask for some samples.

(Laughter)

CHAIRMAN MURRAY: It's too early.

MS. KRAMER: Am I correct that these longitudinal studies, that most of these are identified, so they can keep going back to them for re-consent.

DR. EMANUEL: Yes, but if you've got 50,000 people, re-consent is a two million logistical impossibility. Just sending out a letter to them at $2.00 a crack is $100,000. I mean, these are enormously -- the moment you get to a big number just doing that, not even bringing the people in and having a meeting with them, is a big, big magilla.

DR. COX: -- estimated it would be two million to go back and do it, right?

MS. KRAMER: Going back to this chart, a couple of things really concern me. Number one, you

said in terms of the newborn screening, because it's mandated --

MR. HOLTZMAN: In certain states.

MS. KRAMER: In certain states, exactly.

Well, I'm concerned that there's a potential there, since it is mandated, that there might not be the same attention paid to consent forms, and what might happen to these specimens down the road, particularly if it's demonstrated that they have some value. I have the same concern about, say, commercial blood banks. It seems to me that commercial blood banks, it's very easy for them to escape any kind of --

CHAIRMAN MURRAY: Commercial blood banks?

MS. KRAMER: You know, where people go and sell.

CHAIRMAN MURRAY: Plasma.

MS. KRAMER: Plasma. I'm sorry.

Does that have value?

MR. HOLTZMAN: What, the plasma?

MS. KRAMER: No, the samples. Can't they take --

MR. HOLTZMAN: I think it would be useful to

find out with respect to the commercial enterprises, which would include the plasmapheresis centers, where I don't think they really do keep samples. That's why they're not showing up here. But the core banks and--Elisa, help me out here--the sperm and embryos, those are largely commercial enterprises, right?

DR. EISEMAN: Yes.

MR. HOLTZMAN: What are their consent procedures, if any, for resale or reuse of leftover stuff in research? I don't know the answer to that. Have they been the source, largely, of the leftover embryos to be discarded which are used in embryo research?

DR. EISEMAN: I'm not sure how you would qualify, like, the Genetics and IBF Institute, if you would consider that commercial. I mean, it's more of a --

MS. KRAMER: It's very commercial.

DR. EISEMAN: Yes.

MR. HOLTZMAN: And maybe commercial may not be salient to the extent that there are for-profits doing the same thing.

DR. EISEMAN: Yes, for-profit.

MR. HOLTZMAN: The issue is, what is their ability to provide samples to others.

DR. EISEMAN: Well, I know Dr. Schulman at the Genetics and IBF Institute is very active in research and has connections with a lot of universities, like the Medical College of Virginia Genetics Department, and a lot of samples -- I don't know about embryos, but he's involved in a lot of research. So I'd be happy to try to find out that information.

MR. HOLTZMAN: With respect to the Guthrie cards, the newborn screening, what we know is that, in many, many states, there is effectively no consent. I mean, what we know, in general, is that we range from everything of no consent in the Guthrie cards in many states, to a very thin consent for use in research of the pathology samples, ranging up through a very thick consent in certain research studies, which articulate any and all of the future research uses.

MS. KRAMER: But is it legitimate to be concerned that, in the future, those Guthrie cards could have a value that is not now known, and that,

therefore, we need to be paying some attention to that?

DR. MIIKE: But I think we need to go back and look at our specific -- we just expanded testing for one to seven metabolic diseases. I'd have to look again, but there either are going to be some restrictions on access -- there will definitely be confidentiality issues around that, and there might be some restrictions on access built into the law. I would guess that there's no uniformity among the states about that, but I'll come back and let you know.

MR. HOLTZMAN: Elisa references the Reilley-McEwen paper from '94, which did a survey, current as of then, on this. If that is of interest, we should just get that paper.

DR. EISEMAN: I have a copy. I would be happy to forward it to you.

MR. HOLTZMAN: Yes. And I don't know if Phil and Gene have updated that work recently.

DR. EISEMAN: No, they haven't.

MR. HOLTZMAN: But I guess I would go back to Larry's stated assumption, and that is that, given the spectrum of kinds of samples and kinds of consent

associated with those samples, does that mean that, at least with respect to the retrospective samples, those previous to whatever we do, that one cannot have something that is uniform?

See, I don't think that necessarily follows from a spectrum that one could accept that fact and say, now how are we going to deal with it in a uniform manner, which is built into Zeke's chart.

CHAIRMAN MURRAY: Let me just try two very rough principles here. One, is you should always be candid when you gather a tissue sample about what your intentions are. The candor becomes a kind of first principle. If you know you're going to use it for research, that's the clear intention, you need to tell people that. If you know you plan to use it for some commercial purpose, you need to tell people that. So number one becomes candor.

The second principle would be, to the extent that research or some non-clinical use is contemplated, you need to have a more robust and full consent to that research. So I think it would be -- that's not a very well articulated principle, but I don't think we need

to have multi-page consent forms for every clinical specimen gathered when there is a vanishingly small chance that it will be used for research.

DR. MIIKE: Just to correlate that, Steve, I was thinking more in terms of prospectively, because retrospectively we're not going to be dealing with informed consent, we'll be dealing with criteria for which people can have access.

MR. HOLTZMAN: Right. I'm also speaking prospectively.

DR. COX: Tom, can I make one comment about retrospective. I think that this will come out. Again, it was laid out in Dr. Weir's paper very nicely. It seems like there's no issue with respect to consent for retrospective samples, but there is, in fact, a really important philosophical and ethical issue. That is, even if it's anonymous, even if it's not linked, should people have the right to say whether they want their stuff to be used or not?

Now, retrospectively, they did not have that right. So we're going to have to come up with the issue. Even if we think that they should have that

right now, what do we do about the thing where they didn't have it before?

Some people are saying, and we have to make this crystal clear, that the samples shouldn't be used if the people didn't have the right or didn't say that they wanted it to be used. I mean, that's at the heart of the discussion with respect to the retrospective samples.

I, for one, do not think it's a hard decision, but we have to realize that that's what many people are asking NBAC to sort of consider.

DR. EMANUEL: Let me just review where I thought we came to last time, because last time when I had put up the charts we had, at least in the retrospective samples, two different columns, one for things collected under a clinical rubric and one for things which were collected under a research rubric.

Actually, what we decided in the course of the meeting is just to homogenize them, that that wasn't a relevant distinction. In fact, the way we were moving was to reduce the number of distinctions and to try to make a uniform rule over the whole of that past pot.

The second thing I would say, is we had, I think, come to a pretty clear idea that there were several decisions we were going to have to make, all of which required, I don't care whether you use the balancing metaphor or whatever metaphor, but clearly positive and negative values on both sides.

This was most clear, I think, in the sense of, if you find the result that's specific to a person and you're doing anonymous research, do you have the right to go back? But we've clearly recognized that, in a lot of these cases, we're just going to have to balance things out, and not everyone is going to be happy with that balancing and the judgment will come out differently.

But I think the same is definitely going to be the case, in looking at the retrospective samples. Things were not done optimally, whatever optimally will be, and we'll define that for the samples to be collected in the future. So some moral compromise is going to be present, and I think we just have to be up front about that.

DR. MIIKE: A brief comment on what you just

said. In already collected studies in which people, say, have not given consent, are you talking about expressly, or by silence, or by not thinking about it?

DR. COX: All of the above.

DR. MIIKE: Because if it were expressly, the simple answer would be, they should not have kept that tissue.

DR. COX: Or they shouldn't use it.

DR. MIIKE: Well, why keep it if you can't use it?

DR. COX: No.

DR. EMANUEL: Well, in pathological specimens there's very good reason to keep it. Malpractice, you know.

DR. MIIKE: Yes.

DR. EISEMAN: There's actually laws and regulations to be accredited and state laws for certain times of retention for tissues for pathologic specimens.

CHAIRMAN MURRAY: As we write the chapter of the report that deals just descriptively with tissues, we probably ought to have subsections. Why is this

tissue taken, why is it kept? Some of the answers are going to be malpractice, or other things. Then we'll also want to talk about, why is it useful in research and what kinds of research projects can be done with it?

We'd also want to ask, descriptively, I guess, and Elisa is going to help us with this, under what terms of consent, or not, was this tissue gathered, and a variety of descriptive subsections in that chapter.

DR. MIIKE: Just a comment. There's a myriad of state efforts to protect medical information confidentiality and in many of these the definition of what is medical information will include these tissues. I am in a battle with parts of my own department, the public health side.

We are the only state that has something called an Office of Information Practice within the Attorney General's Office. We're trying to develop laws for an immunization registry. Other parts of my department are saying, you must get consent each and every time one accesses that registry to send information out to clients to let them know that their

immunization is up.

If those kinds of laws get passed on a confidentiality side, and I think the only exceptions might include therapy, which this is definitely not, we are going to be up a creek in terms of, there's going to be such conflict between individual state laws on confidentiality and informed consent versus whatever you try to do in the research area.

DR. EMANUEL: Well, there was that article, I think, passed out by Melton, that came out in the *New England Journal* talking about Minnesota's law and the Mayo Clinic's records, which highlights at least a particulate -- as an example.

MR. HOLTZMAN: I'd like to plant a seed, following up on Zeke's comment, that as we come forward with this, particular with respect to the retrospective, there's a balancing that we're going to have to deal with.

I was really struck by Courtney Campbell's paper about different ways of articulating the balance. There can be a tendency to articulate the balance

simply in terms of consent versus non-consent in a certain kind of conceptual framework built into there, whereas there is a tremendous sensitivity in her paper, extract from the religious issues, for rather in terms of meanings. It was talking about symbols; I'd rather talk about meanings. That maybe provides, at least in my mind, a much richer framework of understanding what you're balancing.

CHAIRMAN MURRAY: And to that point, in a few minutes we're going to have Jim Wells' and others' reports on the mini-hearings. I think we've got some fairly rich and interesting comments from the different groups with whom we spoke about the meaning of scientific research, the meaning of these tissue samples, the concerns they had, but also -- they have. It's very much in line with the things that Courtney Campbell wrote about.

MR. HOLTZMAN: Right.

CHAIRMAN MURRAY: Elisa?

DR. EISEMAN: I wonder if I could just bring up one more point. That goes back to, I think, where you guys were heading the last meeting when it came

time to trying to identify research done in an anonymous fashion. The reason I bring that up is because, as I mentioned at the very beginning today, the vast majority of tissues are identified or identifiable, so that does lead into how you're going to define how research is done and if there's going to be that barrier which you were talking about.

CHAIRMAN MURRAY: Elisa, were there any substantial categories where tissues were, in fact, already anonymous?

DR. EISEMAN: Not that I came across.

CHAIRMAN MURRAY: Okay.

DR. EISEMAN: There's a category that I didn't put in here, but is in the report, and that's research that generates small collections of tissues, and some of that tissue may be collected in an anonymous fashion, but it's going to be very small numbers compared to what we're talking about here.

CHAIRMAN MURRAY: Thank you.

Any other questions for Elisa?

(No response)

CHAIRMAN MURRAY: Once again, a superb job.

We look forward to your filling in the blanks as best you can, but this is already very impressive and allows us to offer suggested policies, not just on our imaginations of what kinds of tissues are out there in which hands, but on some piece of evidence.

Will you be able to stay, or are you running off?

DR. EISEMAN: No, I'll stay.

CHAIRMAN MURRAY: Great. Please don't hesitate to speak up if you think what you've learned will be helpful to our deliberations.

DR. EISEMAN: Okay.

CHAIRMAN MURRAY: We're ahead of schedule five minutes or so. Now, in this part of the meeting, Dr. James Wells will be presenting. I think I see at least one of your colleagues here.

DR. WELLS: Yes. Dana Karr is also here.

CHAIRMAN MURRAY: Hi, Dana. Please feel free to join in. If you wish to sit at the table, Dana, go ahead.

And Sean Simon and Henrietta Hyatt Knorr will also participate to represent these mini-hearings, so

we're delighted to have your comments as well.

Jim, the floor is yours.

REPORT ON MINI-HEARINGS: CLEVELAND, BOSTON, MIAMI

By James Wells, Ph.D.

DR. WELLS: Well, it's no problem starting early, because on Sunday morning there's little traffic, so it's easy to be here in plenty of time.

I was actually meeting in this very room earlier in the week and people were sort of filtering in during the meeting, talking about the bad traffic. Someone said one of the advantages of living only 20 minutes from NIH is that it only takes an hour to get there.

(Laughter)

DR. WELLS: So I am here to update you on the progress with the mini-hearings. Since I was last here we convened three forums, three mini-hearings; one in Cleveland, one in Boston, and one in Miami. The Cleveland meeting was a group that was African Americans, the Boston meeting was primarily elderly, people over 65, and the Miami meeting was, I guess, a more general, mixed group, that happened to be entirely of women.

That was not exactly by design, although we have often relied on the commissioners to help us to make contacts in the locales, and this happened to be a person who was affiliated with the Democratic Women's Club. So many of the group were members of that club, although not all of them, by any means.

MS. HYATT KNORR: And my understanding is that almost three-quarters of them were Jewish, and I think that's of interest because of some of the issues that were raised earlier.

DR. WELLS: Yes. Good point.

We shared with you our reports on these three mini-hearings and presented another table, as we did

last time, kind of summarizing things. I will be glad to entertain any questions about that. I've tried to do a couple of things in my remarks today. I think Dr. Murray asked us to think about conclusions and recommendations about the potential of this technique as an evaluation tool, and I guess potentially future uses. Or maybe I'm just reading that into it.

CHAIRMAN MURRAY: No, that's fine.

DR. WELLS: All right. So I'm prepared to do that. So I can briefly do that, then spend whatever time remains answering your questions and discussing what we brought up.

I will preface my comments in saying that I know that all along we have tried to look at these mini-hearings as an opportunity to look at the diversity of opinion that we find in these groups, and I think that will be reflected in the final report. It's sort of difficult to draw conclusions which are, perforce, generalizations and, at the same time, include all the diversity.

So I guess, as I'm kind of going along, in making these generalizations, please understand that,

where there are important divergences or where there's important diversity of opinion, we will reflect that in the final report.

We tried to draw conclusions in five areas, which I think cover the kinds of questions that have been asked in the mini-hearings.

1. Consent and ownership of tissue

2. Consent to use, privacy and confidentiality

3. Potential stigmatization of ethnic groups on the basis of genetic research

4. Third party concerns

Something I call third party concerns, which has to do with either notification of family members or consent by a family member.

There is a third area. What is the third area?

MS. KARR: For people who can't make decisions for themselves.

DR. WELLS: Oh, yes. That's right. For people with limited capacity to give consent. Actually, I have six areas.

5. Sponsorship of the research

6. Safeguards

DR. WELLS: So let me begin with consent and ownership. Our first conclusion, and I think we shared this one with you on the basis of the first four, is that the general public does not fully understand the consent process. They often feel pressured to consent to procedures because of little time or fear of being denied care and, as a consequence of that, I think, in general feel unable to fully think through the issues involved in providing consent for any procedure.

On top of that, the disposition of tissue -- and this is how we've made our conclusion, on the basis of these groups, anyway, the disposition of tissue is never discussed with patients. So they are totally clueless as to what will happen to their tissue, or that anything could happen, or that anything other than immediate disposal is even a possibility.

I think, actually, if I can find it quickly, I will share with you. One of the quotes from Miami is, "I would be very surprised to find out that tissue that was taken from me after it was tested wasn't just

dumped."

It was the very first thing. We open the discussions typically by having a discussion about, what is tissue, what can you understand from tissue, and beginning to talk about what kinds of tissue could be taken and stored. This is the first response out of the mouth of this particular participant. So obviously this is not something that people are aware of.

DR. MIIKE: At the end of the session, was that one of the ones who didn't trust the government anymore?

DR. WELLS: Well, I wouldn't say that we had changed their mind. Trust was not high.

But what we did find, was that the public wants to retain the right to specifically consent to future use of their tissue, but usually they're willing to relinquish ownership at the time of consent. So they want to be asked, even if the future use may be indefinite. If there's a possibility it would be used, I think that we found most people would want to do that.

DR. EMANUEL: I didn't recall that conclusion

from the first three hearings. I mean, when I was reading it, that struck me as a difference.

DR. WELLS: Yes. Well, I think that it's possible that maybe we were hearing that a bit more strongly in the last three. I think there was some element of that. But I was about to say that this was one where there's sort of an interaction between some diversity of opinion and people's ignorance of process.

MS. HYATT KNORR: Yes. I was going to say, I think what we heard in the latter meetings was somewhat more contemplation of the issues in the sense that people really thought about -- once the issue was raised, they thought about it in a much more intense way than some of the earlier ones.

I think that was more so characteristic of the group and the order in which we have them rather than some dramatic difference between the groups. I think if we had prompted the earlier groups a little more we might have gotten the same answer.

MR. HOLTZMAN: Okay. There's also a range, it seems to me, between someone saying, in principle, I need to have given consent because of lah, dah, dah,

dah, dah, the way we say bioethicists argue versus someone basically saying, gee, if they're going to use it, it would be nice if they asked beforehand. Kind of, what's --

DR. WELLS: I think more of the latter, is my feeling. Yes.

MS. HYATT KNORR: I also think if we looked at the transcripts we would notice that, even though the interview guy, per se, was the same, I think you may have inadvertently asked more for that kind of information.

DR. EMANUEL: He warmed to the subject.

MS. HYATT KNORR: Yes. That's a good way of putting it.

DR. WELLS: We could say he got better at running these particular groups. Yes. But I think that's the case, if people want to be able to believe that they've had a say.

Also, I think because people don't understand the process well it's difficult for them to distinguish between tissues taken specifically for research and tissues taken for clinical purposes. Not that they

can't distinguish that, but once they were thinking about giving their consent, they're thinking about prospective consent, and it was hard to get them to distinguish between concepts such as, that it will be for a specific purpose as opposed to kind of a blanket consent, because they're not used to thinking about these issues.

DR. MIIKE: I think that distinction is important. People are going for routine operation and are not thinking about tissue being used for research, so it's coming as a surprise to them. So it's not surprising to me that that they would say, hey, you know, if I had known that then I would want to be more involved in what happens.

DR. WELLS: Right. And I think people don't understand the idea of consent entirely, or what their rights are to consent, or that perhaps the future use of tissue would be a separable issue from whether they want to have the surgery, given the potential harms and benefits, that other things in the document could be checked off, scratched off, or consented to or refused, and still the rest of the things could go forward.

MS. HYATT KNORR: Yes. I also think that those individuals who have participated in research usually have a serious conditional illness at the time and the surgery was related to that, so their focus was on their getting better rather than on their participating in research.

DR. WELLS: And I will say that the Boston group was particular productive. Because they were elderly, they had had many more procedures done, so they were more aware of the process. A couple of them were a bit more militant as to what you could assent or refuse to.

MS. HYATT KNORR: But I think it was not only a function of age, I think it also had to do with, in that group they were all volunteers of one sort or another so they were a particular kind of group of what you call elderly. As a matter of fact, I would not have thought of them as elderly, because they were very active.

MS. KRAMER: Jim.

DR. WELLS: Yes.

MS. KRAMER: Then would it be fair to conclude

that, for the most part, people have never thought about the issues and are, therefore, initially more permissive than they end up being once you have generated a conversation and they begin to think about it? No?

DR. WELLS: I'm not sure that's the case.

MS. KRAMER: No.

DR. WELLS: Partly it's difficult to distinguish because we start out asking them about anonymous, so I guess they might naturally be more permissive there. As the discussion goes on there's sort of more layers of complication that occur.

MR. HOLTZMAN: That's what strikes me in what comes out. We start here with having the range of issues, some of us having read the literature and thinking about the issue, you watch it go through. They don't think about it, don't know. They're exposed to the notion of the research, and then you get the diversity of the -- it's mine, I want control, to it's no more related to me than the used car part -- use it for research, I don't care. So you really get the diversity.

DR. WELLS: Now, certainly it raises a concern, but I'm not sure whether, as it progresses, they actually become less inclined to say that they would consent.

MS. KRAMER: So it's not going to necessarily affect whether they give consent, it's just that they want to be asked.

DR. WELLS: Yes. Yes, I think that's true. I think that's true.

CHAIRMAN MURRAY: And, if I heard you correctly, they don't remember being asked.

DR. WELLS: They certainly don't remember being asked. I don't think, out of 70- or 80-odd people, we've ever had anyone who said, I was asked about the disposition of my tissue, or it was ever discussed.

CHAIRMAN MURRAY: If we went back and looked at the forms they signed, we'd probably find pretty uniformly that they were asked something.

MS. HYATT KNORR: Oh, they remember that.

CHAIRMAN MURRAY: They remember signing something.

MS. HYATT KNORR: They remember that they signed something, but they didn't remember what they signed, period.

CHAIRMAN MURRAY: I don't intend that as a criticism of the people, I intend that as a reflection of the process.

DR. WELLS: Oh, quite often they said, I didn't read it. And quite often people complained about the fact that it's given under conditions under conditions of high anxiety and stress, any consent, and that makes it more difficult to give it their full attention and really understand.

MR. HOLTZMAN: As a measure of the currency of this issue, did anyone happen to see *E.R.* this week? The case was of a young child that came in with organ reversal. He'd been in a car accident. So they wanted to take a blood sample to do a genetic study. The child is in the process, essentially, of dying, and that's all the father is thinking about.

Now they approach him on the ability to take the blood sample. He's handed a consent form, which is

about -- and he sits there, it's about six pages long, single-spaced, and he sort of leafed through, uncomprehending in about two seconds, and then, oh, there's where I sign.

DR. SOBEL: But the critical factor in that story is, when the boy dies before the blood sample is actually taken, it becomes clear that the father thought that -- it was never really clearly stated to him that this was a research study, that it was not going to specifically help his son.

MR. HOLTZMAN: That's correct.

DR. SOBEL: He had the impression, when he was presented with the story, that it was going to help his son. I'll do anything to help my son.

MR. HOLTZMAN: Right.

DR. SOBEL: When it was no longer going to help his son, he then asked the question -- and did not consent, until later in the story.

DR. HANNA: I notice in your Miami group that one person alluded to the issue of computerization, computerized data bases. Has that not been raised by very many people?

DR. WELLS: Oh, that's been raised by everyone.

MS. HYATT KNORR: It has been raised. Anyone who has any level of sophistication in the area certainly is aware of that. In Hawaii --

DR. MIIKE: Remember the Hawaii guy. The guy was so into computers, I think he was out of touch with reality.

(Laughter)

DR. MIIKE: It's one thing to say that there are myriads of data bases around in little research institutes, it's another thing to say that one person or one organization can tap into all of those. The connections are missing. But he was convinced that, if it's there, you can do it.

MS. HYATT KNORR: I think he was very concerned about this.

DR. MIIKE: His whole focus was on computers.

DR. WELLS: But I think that's another area. Maybe I'm contradicting Henrietta a little bit here. While people are aware that data bases are computerized, they don't seem to have a great

understanding about how things may or may not be linked.

I mean, we had a number of people like the one that Dr. McEwen is referring to, who thought that it would be nothing for you or I to walk up to a terminal and put together all the information about them, which, even if you wanted to do, I think most of us are aware, would be extremely difficult.

MR. SIMON: They're very into cross-analysis of data base, that anyone would be able to, with the right computer wizardry, be able to cross the proper data banks in order to get whatever information they needed about anyone in the United States, basically. There's about one of those, almost, per group.

CHAIRMAN MURRAY: I got a letter from an old friend this week who's in a totally different world, he's a lawyer in Columbus, and he's been on the campaign to -- it's a little off the track, but not entirely. He's been on the campaign -- apparently when companies -- there are these transfer companies. If you own stock -- this is hypothetical; I don't own any stock. But if you own stock and you get paid

dividends, they send your check out. But, you know, a considerable percentage gets returned.

These companies, they'll send it out a couple of times and then they'll just hold them and earn the interest on them. This guy is infuriated at this practice. So he found out that in other -- he's gotten, actually, a law to not tolerate this anymore. But it typically takes about 90 seconds to track a name down on one of the various data bases.

DR. WELLS: Credit data bases.

CHAIRMAN MURRAY: Your address can be on a publicly available data base. Your current mailing address, et cetera, can be obtained, on an average, in about 90 seconds with a computer search.

DR. WELLS: Yes. I could do it on AOL. But these people are not only worried about having their address found, it's that once you have their address you can find out everything else.

CHAIRMAN MURRAY: You still have to link everything else.

DR. COX: This is, at least for me, very, very important. You made, if I paraphrase you correctly,

and what I heard in San Francisco, the public wants consent, to be given the choice to give consent, but, and even though they didn't know what was happening with their samples, when they heard about it they said, give me the choice to give consent.

But then it's the issue of relinquishing ownership, or at least still wanting to contribute to the public good with respect to research. So they may not have known what was going on with their tissues. They were surprised by that. But it wasn't, as soon as they found out they weren't going to let anybody do research anymore.

I'd like to bring that up because I think that that's one of the main motivations for some of the views of certain stakeholders, of not informing the public, because if they actually knew what was going on then they wouldn't let research go on anymore. And I think that, for me, one of the really important things that came out of all these hearings, is that none of the testimony or the statements that we've heard is consistent with that.

I mean, some of the people may have been more

cautious than others, but it certainly wasn't, if you were going to draw general conclusions, that the overwhelming view was that when people heard about this they said, well, I'm sure going to shut down research. I mean, I think that's really -- I must say, it was a prejudice of mine going in. Maybe that's why I liked the conclusion, because it confirms what I found in the beginning.

MR. HOLTZMAN: There's two ways you can go with that. Let's assume my sole stake is making sure research goes on. I now gain confidence, as you just said. I can make one of two conclusions. Therefore, I should have robust consents associated with everything and that will be wonderful and I'll get good consents, or the alternative is, given that the overwhelming majority of people would consent given the choice, that, therefore, pragmatically I can use a much thinner kind of consent, or what did you call it?

DR. EMANUEL: Presumed consent.

MR. HOLTZMAN: Presumed consent. So I think that's one of the things that we need to think about.

DR. COX: Yes. But I think there is a

significant fraction of people that are against sort of changing any of the rules for consent because of this fear that people won't play. I just don't see it up there.

MR. SIMON: People basically wanted to vote. Some people would have studied more on the issues before they voted, but either way, they essentially wanted to vote. The analogy being the democratic process, they wanted to have a hand in the matter.

MR. HOLTZMAN: Okay. Well, 100 percent of the people want to have the right to vote, and then only 40 percent exercise it.

MR. SIMON: Exactly. I think there's a lesson.

MS. HYATT KNORR: But I think there's another point that has to do with that as well. I raised the issue, I think, at most of the meetings. What about samples that have already been taken in the past where consent has not been obtained? And there was uniform agreement, and I don't think anybody disagreed, that whatever it was, it should not be wasted. There was a really strong feeling about the public good and the use

of these samples.

DR. COX: Even when the people were shocked, that they didn't know about something, it didn't take away this feeling of the public good. To me, that was --

MS. HYATT KNORR: Right. And another place where that came out was when the issue was raised about possible profit-making. Overall, I think people do not feel that, even though it was their tissue, that -- profit-making, that that would change anything, really, as long as it was good for people.

DR. WELLS: Right.

CHAIRMAN MURRAY: I had a slightly different read on the Cleveland group. But I'm concerned; we've got about 25 to 30 minutes left in our session.

DR. WELLS: Okay.

CHAIRMAN MURRAY: And we're preventing you from going through your presentation. We're having a very good conversation.

DR. WELLS: Well, we've actually covered some of the additional points, but I'll go over them quickly, just to reiterate, to jump ahead to

sponsorship, that's what Henrietta is bringing up. What we concluded, or the way we wrote it, was that the general public sees the benefit of genetic research to society, regardless of who sponsors or who conducts the research.

Dr. Murray is right. The most dissent we probably heard about that was in the Cleveland group, where there was some concern. We asked two kinds of questions. The one, was do you make a distinction between an academic researcher and a researcher in a biotech or pharmaceutical company? There we did get some distinction and some preference for the academic researcher, and really nowhere else.

The other question was, does it matter who sponsors the research, who pays for it, a for-profit or the Federal Government, and we never found too much concern over that difference. We often heard comments of the sort that said, as long as they're producing something good, as long as the drug will have a benefit or as long as the research will produce something that will help people, then it doesn't really matter.

I think, in general, again, with perhaps the

exception of Cleveland, people just didn't make any distinction in the ethics of research that you would find in the different places or under different sponsorship. We never heard any concerns about that.

There are another set of issues having to do with privacy and confidentiality that we've already kind of overlapped a bit. That is, we felt that, based on these meetings, we could say the general public is comfortable with the confidential use of stored tissue, including linkages with demographic information such as sex, age, and ethnic group.

We never found anybody who was very concerned about linking it with other information, certainly as long as their name was not associated with that linkage. Perhaps more concern if there was a possibility of going back to the name, and that's where some of the people who had more concerns about cross linkages of data bases and so forth expressed their concerns, because they obviously didn't -- we've had people say, even if you had rules about linkage, well, we don't trust people to follow them. So there's always some small group of people who didn't trust

anybody no matter what, but, in general, people, I think, were not concerned about those linkages.

One difficulty I think the public has in thinking about this issue is, in differentiating between a linked study or any research study that may have a general benefit to the public as opposed to something that may have direct benefit for them. So one reason people don't necessarily even want to have an honest research is that, if there's something that's found out about them, they'd like to hear about it.

So that sort of overrides the concern, even though -- and once again, as we got more sophisticated in running the groups I would say, well, it may well be that research will be done because there will be no direct benefits to you.

I think that was difficult for people to grasp, that notion that the tissue was taken, obviously some sort of direct test was done that, for clinical reasons, might have some direct benefit to them. Then research might be done and, in all likelihood, nothing would be found that would be a direct benefit. I think that very small probability loomed large in people's

minds.

DR. MIIKE: Just one comment on that. I believe it was, and I don't know how all groups were -- to me it was a sophisticated answer in the sense that they didn't really expect to individually benefit. They didn't see any great probability of their being individually benefitted, but if the research found benefit for those types of people with those diseases, that that answer was taken back into the medical community and they would benefit from that.

DR. WELLS: Yes.

DR. MIIKE: They had that perception.

DR. WELLS: Yes. Right.

DR. MIIKE: That's pretty complicated.

DR. WELLS: It was. There was somebody -- I think we quoted it in the last table that, in fact, somebody spoke of this indirect benefit, that through the medical literature, I believe they even said, that this would be disseminated and they could actually benefit, even in that indirect way.

CHAIRMAN MURRAY: I want to see if I understand something else I thought I just heard you

say, that you detected a pretty strong sentiment that if there should be a finding in the course of research that could then -- an unanticipated finding, that could then be beneficial back to the individual who was the origin of the sample, that people would want to have that connection.

DR. WELLS: Yes, people would want to.

We did have some discussions, I think most strongly in San Francisco, that people recognized there may be difficulties in doing that. Procedurally, some people in San Francisco actually expressed the opinion that might be an excessive burden on research to have to do that. But, in general, I think you're right.

CHAIRMAN MURRAY: If it entailed a trade-off between an additional incremental protection of individual privacy versus the possibility of, if something should be found that might be useful to afford that, the possibility to walk back, did you get a clear sense of how people would want to make that trade-off?

DR. WELLS: Well, my sense is, yes, that they would trade some confidentiality or some protection for

that information, for that knowledge.

CHAIRMAN MURRAY: Would I be off-base if I sort of tried to describe that as a sense that, if I make this gift of my tissue, I then have a kind of relationship with the researcher or the research, so that --

DR. EMANUEL: I don't think it's relationship based, do you? I think it's sort of the idea that you've done your contribution and this is the -- if there's going to be a benefit, then you should know about it, right? That's the sort of -- while you're not expecting that return, if it comes out, that's the appropriate return on the gift, as it were.

MR. HOLTZMAN: But is it --

DR. EMANUEL: But that's not necessarily a relationship.

CHAIRMAN MURRAY: Well, in the process. In the same way that what I donate --

DR. EMANUEL: Right. But I think what I hear over and over from your summary of the hearings is that this concern of privacy, it's not as big a concern as one might have expected. That, yes, it's out there,

but clearly there's a health benefit and that's definitely going to outweigh the privacy concern. They don't feel that threatened by it.

MS. HYATT KNORR: As long as it doesn't have anything to do with the insurer or the employer.

DR. WELLS: Right. That's the other one under privacy and confidentiality. That was the clearest thing we heard anywhere, was they do not want insurance companies to have access to findings on research about their stored tissue. That was pretty clear.

MR. HOLTZMAN: It seems to me the idea of, I want to know if they can help me, probably is not grounded in this gift or contribution. I mean, in general, I think all of us, if there's something we're suffering from and something could help us, we'd like to know about it. So in this context where there is the potential for directly linking, you want to know about it because it's possible to know about it. It's nothing more than that. Okay.

The second thing that strikes me in terms of privacy, confidentiality --

DR. EMANUEL: I think of it differently.

MR. HOLTZMAN: No. I think there are two cases. Let's remember the two cases. One, is for the illness, in general, which you might suffer, and then there's the case which I think you brought up last time, which is they serendipitously find out something specifically about you that doesn't apply to everyone else in that category. I think we have to distinguish those two cases. Tom and I think we're talking about the first, and you may be talking about the second.

DR. EMANUEL: Okay.

MR. HOLTZMAN: Because I do think those are two different kinds of cases.

DR. EMANUEL: Because I do think

MS. KRAMER: What concerned me the last time though was, was there this sense that the researchers have a responsibility to those who have donated the tissue to apprise them, just a general responsibility?

MS. HYATT KNORR: I did not read it that way. I read it much more like, if it is possible for me to get this feedback and not give back too much, or any, of the confidentiality, I would certainly like to know because it would then help me or my family. Did we

discuss Zeke's idea of the wall?

MS. KRAMER: You did.

MS. HYATT KNORR: Yes, we did.

DR. MIIKE: I don't think that's such a big issue, because there's going to be very little or a very small probability that the information will be generated that will benefit the individual.

DR. WELLS: Right.

DR. MIIKE: It's the other stuff, which is that we have information but we don't know what it can do for you. But it may raise concerns about probabilities about disease, and we can't do anything about that. In that example, in that particular area where there's information that causes that kind of dilemma, you get sort of a mixed response. I think many people -- I mean, it just gets back down to, yes, I'd like to know, or no, I don't want to know. So there's no really --

DR. COX: But I think you're right on the target here. What is benefit? Most of the time when people said that they wanted to know stuff it was in the context that there were clear options that were

open to them with that kind of information. I mean, most people don't think about information as not having options hooked up with it. That's another thing they can't believe, I think.

MS. HYATT KNORR: But in Hawaii the issue came up, such as Alzheimer's. The response there was, I'd really like to know so at least my family or I can prepare for it.

DR. COX: Oh, sure.

DR. EMANUEL: Right.

DR. COX: When there's not options, then it's a mixed bag. But it's hard for me to imagine, if there was really direct options, that I could do something to save my life and I knew -- like, if I didn't get out of the street I was going to get hit by a truck because it was just coming down, I want somebody to tell me that the truck is coming. So I can't imagine somebody not wanting to know that.

DR. WELLS: The next category was a series of questions about stigmatization of ethnic groups. I think in that, people were not concerned about the stigmatization of ethnic groups, although they

recognized the potential for this to happen. Conversely, they did see the potential benefit to ethnic groups of group-specific genetic research and felt that outweighed any potential harms.

I mean, generally we did get at least some people in the groups who said, oh, yes, that -- often people spontaneously talked about Tay-Sachs or something like that. They knew of specific diseases that were associated with particular ethnic groups, and often recognized that this kind of research actually was potentially a benefit for those groups.

I think we talked about this last time. You could get people to speculate in sort of a general sense about, something prejudicial could result from this, but nothing concrete and no real strong sentiment, no strong concern.

CHAIRMAN MURRAY: The group in Cleveland--I only have the one experience, I didn't attend the other meetings--very early on mentioned Tuskeagee, which is highly salient. They also mentioned the Cincinnati radiation studies. So they were very attuned to potential misuses of people in research. But they also

were very supportive of research on ethnic groups, including African Americans.

I wrote down, and I hope I've got the quote correct, "The more we know about ourselves the better we'll be." It was very insightful commentary, I thought, and a number of comments about how, in general, they were very, very much in favor of research, even research on particular ethnic groups. They did talk about accountability, researcher accountability, and how we would review research for it. I don't know if you plan to cover that expressly, Jim.

DR. WELLS: Yes.

CHAIRMAN MURRAY: But my impression was very consonant with what you said.

MR. HOLTZMAN: So Tom, to someone like yourself, and maybe Zeke and some of the other professionals in the field, who are very cognizant and keep up with the literature on this whole subject, which seems to be very, very sensitive to the notions of stigmatization in groups, and whatnot.

As you attend these meetings, as you read the

transcripts, or whatever, do you find what the common person is saying and their attitudes are very different than the literature?

CHAIRMAN MURRAY: In the limited sample I have, yes.

DR. WELLS: I think that's true, too.

DR. EMANUEL: The most important thing is just the weighing of the different concerns. We--the literature, that's the "we" I'm referring to--weigh issues of consent a lot more and suspicions of dangers a lot more, and I think the public doesn't look at it that way, by this insurance/employment issue, which I think you're going to come to.

MS. KRAMER: It's interesting. I'm going back in my mind to when Dorothy Wertz was here, eons ago, right? And I remember her saying specifically that, even though nobody has ever polled or surveyed on these specific issues, that her gut feeling is that the public won't care as long as the insurance companies don't know. It's interesting, because it's really what's being borne out.

DR. WELLS: Right. Well, I think that's one

clear place where they see potential harm to them. No matter what the legalities are or whether they waive and have given insurance companies the right to take a look, they see the potential for direct harm to themselves. I don't think there was any other area where people so directly and clearly felt the potential to be harmed by breach of confidentiality.

MR. HOLTZMAN: I raise that question because, coming from outside of the professional circle and then diving in and reading a little bit of the literature and then listening to this, it really strikes me that the literature, apart from the insurance, is conceiving of the terms of the way it thinks about this and the way in which it's probably different than people think about it. That's what struck me about the Campbell paper, is that the Campbell paper maybe is closer to how people think about this because, at least for me, offers a better understanding of how people are reacting.

DR. EMANUEL: Maybe. I'm not sure I would put it that way, but I see what your point is.

CHAIRMAN MURRAY: And we have to be cautious.

We don't have anything like a population base random sample, which I think for very good reasons we decided didn't make a lot of sense because you'd have to spend so much time explaining what this was all about that, by the time you got to the questions, it was unclear what meaning you could derive from the answers.

But, nonetheless, we do have a cross-section of the United States, a variety of different communities, a variety of different ages, sexes, groups, identities, and we've gotten some very interesting answers.

DR. WELLS: And I think that may account for the different between our sense of what people's desires for privacy are because in our discussions we really got into how they optimize privacy against potential public good, against potential personal good, against potential -- it makes it difficult to sort those things out, but, in fact, I think gives a little richer view of what people think about these things.

We did discuss third party concerns. We had asked people about disclosure to family members. I think that, in general, we could conclude that the

general public believes it's the right of the tissue donor to choose whether or not to disclose to anyone, including family members, findings from their research on stored tissue.

I think in the first groups we had a lot of discussion about these things, and sort of moved this question to later on because it tended to -- the questions of family, what would go on, and so forth, sort of took over the rest of the discussion, because it just adds another whole set of permutations that were difficult for people to think about.

But, nonetheless, I think it was clear. Certainly we would ask this question and people would express a lot of concern if someone else were contacting a family member or something about the potential for genetic disease, but then we got into all the issues of whether you're talking about a specific, direct, and treatable condition or whether you're talking about a propensity and how that interacted with family dynamics, and so forth.

CHAIRMAN MURRAY: I was getting a little bit lost there. Could you give us a quick summary of what

attitudes you discerned about notifying family members? What I heard was, you basically don't tell the family members.

DR. WELLS: You don't tell the family members.

CHAIRMAN MURRAY: You tell the person.

DR. WELLS: You tell the person and they may or may not choose to do so, or they make the judgment on what to do with that information.

CHAIRMAN MURRAY: Did you get into questions where the person, the original donor, was now deceased?

DR. WELLS: Yes, we did. We actually had a scenario about someone with a brain condition. I'm not sure if we got enough information to --

MS. HYATT KNORR: I don't think people reacted to that very much.

DR. WELLS: Right.

MS. HYATT KNORR: When you'd tell somebody in that case.

DR. EMANUEL: The typical problem of trying to make them look forward and then look at a series of -- I mean, the more hypothetical the situation the more difficult it is for people to imagine, and then you're

asking them for a series of judgments. That's a classic thing. Survey people tell you, garbage in, garbage out, and don't rely on it. The further it is from their experience, the less useful it's going to be.

DR. WELLS: Right. But I think the answers, in general, would be the same. I mean, I'm just trying to think if there's -- I think people had different concerns about that. I mean, in fact, they raised those. Why did they do this test, and why is it coming up now, 30 years later? So the scenario was more problematic than the concern, I guess.

We also asked them the question about, if someone has limited competence to consent to use of their tissues and I think people just saw that as a real straightforward, legal guardian, power of attorney issue. It was hard to get them to think about that any further than that. It's just that, well, that's straightforward. They just ask the parent of the child, or a sibling, or whatever, the child of an older adult.

Finally, we asked them about safeguards. I

think, as I told you last time, the general public does not have an abiding faith in any one group to protect medical information and to protect the confidentiality of medical information.

We asked them about the governmental medical profession/legal professional institutional review boards. We got opinions all across the spectrum as to trust, and none of those really rose to the top, although I think people were sympathetic with the notion of IRBs. There were some groups where sort of the IRB won out, and others where physicians won out, and others where -- but it was very mixed.

MR. HOLTZMAN: Did most people know what an IRB was?

DR. WELLS: No, we had to explain that. We had to explain it. We never called it an IRB, we called it an ethics review board.

DR. EMANUEL: I've actually been in contact with ABC to try to convince them to do a story on IRBs.

DR. MIIKE: And they said N-0.

DR. EMANUEL: Well, no. They need something

to peg it on to, as usual, you know, with TV. But they didn't even know. The producers didn't even know. It was quite interesting, despite their coverage of a lot of science.

DR. MIIKE: The reaction was, once they knew there were IRBs they thought it was a good thing.

DR. WELLS: They thought it was a good thing. They thought it was a good thing. But they knew so little about it. I remember, in one of the groups in Hawaii, they started down this path of conversation as if there was one sort of mega-IRB that would be here in Bethesda, or something. We had to --

DR. MIIKE: They thought it was all computerized.

(Laughter)

DR. WELLS: Right, it was all computerized. But once we talked about that being a local kind of thing -- I think perhaps this is not going too far beyond the data to say, the more local, the better. I mean, the other side of it is, people were often willing to say, well, my personal physician is someone that I trust to deal with medical information. But

then you have to bring up on the other side, well, that person may not always be the one involved in research.

We did ask people to identify who they thought desirable members of IRBs would be, and I think, in general, they identified the kinds of people who are typically on an IRB. Although there was one answer that came up very often, and that is that IRBs should have ethical people on them. Not ethicists, ethical people.

DR. EMANUEL: They grasped that distinction.

DR. WELLS: Right. Right.

(Laughter)

DR. WELLS: I don't believe that's required in the regulations, actually.

(Laughter)

DR. WELLS: Make sure to include those on the IRB.

MR. HOLTZMAN: Did you notice that that led one group to conclude absolutely no lawyers?

(Laughter)

DR. WELLS: That was our doctor sample.

MS. HYATT KNORR: Some people didn't trust

their ministers either.

DR. WELLS: Yes. Although clergy was a common nomination as a group that ought to be on IRBs. We did have that in one instance.

CHAIRMAN MURRAY: In Cleveland they also mentioned "highly ethical people." They wanted people on the IRB who were not affiliated with the organization doing the research.

DR. WELLS: Yes. Yes.

MS. LEVINSON: All the people or --

DR. WELLS: I don't think that was the case. I just think --

MS. HYATT KNORR: There shouldn't be a conflict of interest.

CHAIRMAN MURRAY: Right. I read a substantial.

MS. LEVINSON: So in other words, one is not enough.

DR. WELLS: Probably one is not enough. Not only in Cleveland, but elsewhere, people felt that groups being studied ought to be represented. We didn't get into the mechanics of that, but they had a

strong feeling that if, in particular, an ethnic group -- and even if it wasn't an ethnic identification, everyone identified themselves as, a group of people like us would want to be represented on that group, if that were the group being studied. So I think that was a fairly general finding.

That's my six topics. So I have a couple of minutes.

DR. EMANUEL: I have a challenge for you.

DR. WELLS: Sure.

DR. EMANUEL: As much as you bemoan this, and as much as you have warned us against it, it occurred to me, we have variously talked about the possibility in the future of doing a survey, either for our next topic of confidentiality, et cetera.

Now, I know you've got a long list of caveats about educating the group. Are there 5 or 10 questions you could come up with, if we locked you in a room for 8 hours, that might be useful in a survey format as opposed to a focus group format for thinking about this?

DR. WELLS: Yes. I think the answer to that

is yes.

DR. EMANUEL: And would you mind burning those eight hours doing it?

DR. WELLS: No.

DR. EMANUEL: Because I think, first of all, it would be extremely helpful for me, having not participated in any one of these, to hear what you think. At the conclusion of focus groups, you usually don't give that as data but you give that as preliminarily to giving us our survey questions.

So I was hoping that you might get 5, 10, or 15, whatever the right number is in your view, of questions that we might be able to, if we ever get the money and the inclination, et cetera, included on the survey, and even if we don't, we might be able to buy some survey time on someone else's survey, because I think that would be helpful. I mean, I have some ideas of the three or four that I might ask, but I haven't sat, as I said, through any of the focus groups.

DR. WELLS: Well, I think 3, 4, or 5 would be much more difficult than 30 or 40.

DR. EMANUEL: Right.

DR. WELLS: Because you could probably do a half a dozen or more in each of these areas --

DR. EMANUEL: I understand.

DR. WELLS: -- just to flesh out or look at the prevalence of some of these things.

I think there are some areas where it's pretty clear-cut that there were strong opinions and you probably wouldn't need to repeat that in a survey. I think some of those where there's more diversity, where you could perhaps now feel more comfortable in putting together a set of kind of stipulations about what the circumstances are, and then ask questions about, under these circumstances, would you, and then have concerns about confidentiality, privacy, and so forth.

DR. EMANUEL: I think that would be great, if you could do it for us.

CHAIRMAN MURRAY: You want him to do the five or six?

DR. EMANUEL: Well, I think 30 is impossible because, under no circumstances, if we're going to do a general survey -- you've got 50 to 70 questions, 30 would be half of it, and we're going to have at least

one or probably two other topics. But I think 10 or 15 is doable, and, even if we never do a survey, it's at least within the perception of buying space on someone else's survey, might be possible.

DR. GREIDER: But that depends someone on what the motivation is. The large number of areas that were covered here, if you were to take one of those, like you just mentioned confidentiality, or one of the other ones, then you could come up with 10 questions just in one of the areas rather than 10 questions in all 6 areas.

DR. COX: But Zeke said, and I think you're right on target, one possible motive would be that some of these things we think are consensus, but it's on a very small sample, so go out and find out if it's true or not. We're sitting around the table right now, for better or worse, implying it's true. Maybe it is, maybe it isn't.

DR. EMANUEL: Well, one area that I think is important is this issue that you've raised several times about, they don't want their tissues commercialized. You think that's uniform. I think if

we really heard that that was an 80-90 percent response, that would be helpful. Second, on the other hand, they don't mind if biotech or pharmaceutical companies make money off of research on.

Third, the fact that they do want to promote research, they don't want the samples wasted, if we found that that was uniform across all, this kind of trade-off of benefits to the group versus confidentiality is another kind of area, this issue of the fact that more research, even on specific ethnic groups, turns out to be beneficial. These are the ones that I've highlighted or circled.

Also, this idea that they're basically suspicious of every single group in the world to protect them from information is, I think, another -- I mean, that's a real problem, I think, for everyone involved in this and something we all need to think about.

When I said I could think of three or four, it was those that I could think of. But I'm sure you have, again, having sat through all of these, other senses that might be very helpful to us.

CHAIRMAN MURRAY: We're running a little over, but I think it's worth running a little over. If you want to ask questions, go ahead.

MS. KRAMER: I was just curious. When you go back to your mind-set when you started and where you are now, were there any big surprises there for you?

DR. WELLS: Big surprises. I think the one that people had a little concern about who sponsored or who did the research, I was surprised. I grew up in an academic world with those biases, and I was kind of surprised that people felt that way. I thought that was more widespread than just the halls of academe, but apparently not the case.

DR. EMANUEL: But also this one about more research on ethnic groups basically being viewed as beneficial, not as a harm or stigmatism. I find that --

DR. WELLS: Yes, totally. Although there were some actual -- for example, in Cleveland, where the group was African American, when Tuskeagee was brought up by one individual, a couple of other people argued, well, it wasn't really relevant so it didn't really

apply. Things had changed greatly and that wasn't really a concern for this particular kind of scenario that we were talking about.

MS. HYATT KNORR: I think that's probably one of the questions though where, if we ever did do a survey, that I would really like to explore because I felt that we didn't have large enough or varied enough, an unrandom sample here, I think, to come to that conclusion. It did appear that way.

DR. WELLS: That would be a harder one in a survey, though. Well, you'd have to be very careful about how you identified -- people who identified themselves.

CHAIRMAN MURRAY: The Cleveland group were from the community.

DR. EMANUEL: You mentioned the Tay-Sachs case. The other possibility is to mention sickle cell, or something. If you have two or three ethnic groups implicated, it might --

DR. WELLS: Sickle cell did come up in the Cleveland meeting, and others.

CHAIRMAN MURRAY: Rachel?

MS. LEVINSON: I'm thinking about the kinds of questions, if you're limited to 10 or 15 or so, which seems reasonable, and perhaps grouping them around some kind of a concept. It will be highly desirable to have the recommendations from this group be able to be translated easily into policy recommendations and that those need to be supported by some kind of consensus.

I can see some directions where you're going that are counter to some general public thought, and if there's evidence from the survey to back up those particular recommendations, it would be very useful.

DR. EMANUEL: The policy --

DR. WELLS: And certainly that makes sense. I mean, if we are going to do this we ought to have enough iterations to be sure that the results that we get from those questions directly answer and allow you to make a decision.

DR. MIIKE: On the question about ethnic groups or other ways of grouping it, it was never my impression that people were against research in that area. There were concerns raised around research that would be done in those areas. That's the assumptions

I've always worked under. It's not that research shouldn't be done among ethnic groups, but the conditions surrounding them; isn't that right? Isn't that what we're talking about?

CHAIRMAN MURRAY: There are at least two kinds of concerns. One, is the misuse of human subjects, whether they'd be harmed or wronged. The second, would be that the information generated by the research might then be used in a prejudicial or otherwise advantageous way.

MR. SIMON: I wanted to make one quick, final point, if I could. One of the difficulties that we came up against that I think may be exacerbated by a survey, or just not answered, is people in this -- the issue of linked samples, using their linked samples in research, is illustrative of this problem.

It was, they would say yes, that they want their sample linked so that they could be notified of advantages, and they would also in later discussions say, no, they do not want it linked because of their primary fear, which was breach of confidentiality.

But when it came down to, what is the

probability and severity of the confidentiality breach versus what is the probability and degree of direct benefit of having the linked sample, they just weren't able to carry out the risk benefit analysis. I didn't think that was surprising.

I wouldn't say that that was something surprising, but it was unusual that you could even get a situation phrased like that, if you could get both situations on the table so they could be seen in one light. It was always one scenario, the other scenario, and somehow they could say yes to both without bringing together the fact that there's a probability and severity.

CHAIRMAN MURRAY: Right. But had some thoughts about the implications of that for whatever policies and practices we recommend.

Stephen had a question.

MR. HOLTZMAN: It's a question to Jim and anyone else who attended these, and it goes to the issue of consent. I think one thing in the sea of uncertainty that we know, is that with respect to any sample taken at any particular moment in time, that the

specific research one could envisage at that time doing with the sample is less than all of the research that could be done with it in the future.

So that goes to the issue of, what does it mean to consent to future uses? Some have argued that it's in the nature of the concept of consent that an open-ended consent is not conceptually possible. Putting that aside for a second, the question I have is whether people, as you indicated, seemed open to the notion, as long as you ask me, it's cool. It could be very open-ended.

When one of them went through the way you can imagine research at some point being done of a nature which you would find offensive, do people still have a sense of identification with the piece of themselves, the sample, such that they would want to be able to control that possibility?

DR. WELLS: Some, yes. Actually, I think we were asked to bring up the tissue of reproductive tissue. In the latter couple of meetings we did that.

CHAIRMAN MURRAY: Other than reproduction tissue.

DR. WELLS: It never came up spontaneously. But we did ask about reproductive tissue and there were some people, a couple in the last two groups, that said, oh, yeah. If it was that I wouldn't really want fetal tissue research done. But it was more categorical. I don't think it was related to specifically -- well, I just think they already had those opinions about those issues and this became an opportunity to express those. But, yes.

MS. KRAMER: I think that this is probably too big a jump to make, but if you go back to the point that you made that they focused on the potential benefit to the group of the research as against the potential stigmatization, and now jump to Steve's question about potential future research that might be done that they might find offensive.

So the question is, I guess what I'm struggling with, is how would they designate that offense; how would they describe that offense? Might they not say, well, but there might be something gained from the research that would be of use to the group, that would be of benefit to the group, so why not let

it go forward? I'm trying to get a handle on it.

MR. HOLTZMAN: Let's put aside the surveys. We are all people around this table too.

MS. KRAMER: Right.

MR. HOLTZMAN: If you get yourself in a mind-set of saying -- I'll speak for myself here.

MS. KRAMER: Okay.

MR. HOLTZMAN: All right. I'm very open to the notion of giving a very open-ended consent to the use of my sample, and what comes to mind are the prospects for research which will be of benefit to mankind--personkind--that I can't even imagine. The only sort of hold-back I find, is that I think of certain kinds of research, and all one would have to think of here is Nazi Germany, and the notion that my sample might be somehow used in such research, I find myself asking questions, to what extent am I implicated in that research if my sample contributes to it, and a sense of complicity in an enterprise which is morally offensive. Maybe no one else thinks this way.

CHAIRMAN MURRAY: Well, complicity, maybe not, but being used in a way that was reprehensive.

MR. HOLTZMAN: But then that question, to what extent do I want to continue to have some notion of control over that which is not possible with a totally open consent.

DR. MIIKE: Well, Steve, I have problems with that kind of scenario because then it sort of leaves out all of the other structural safeguards and things that we've done. That sort of assumes that we're going to be working in a different society or that we don't have IRBs and we have other kinds of things that, when a particular kind of study comes up, that those kinds of things don't get addressed.

MR. HOLTZMAN: Okay. That's good, if we could maybe think along those lines. I'm trying to give as much weight and respect as I can to those who take a very, very strong position with respect to consent in either the logical impossibility or problematic nature of totally open-ended consents.

DR. MIIKE: I think you're stuck with it, in my mind. I don't think you can ever -- I think we can never find a satisfactory thing that predicts what kind of uses come out of those, so you can't just leave

everything around the issue of, when I give my tissue, what kind of consent am I going to give. Something has to happen down the road that safeguards against those kinds of concerns at the front end.

MR. HOLTZMAN: But, again, Larry, I think there are those who have argued that, therefore, you need to continually go back and re-consent. What you've pointed to are other structural mechanisms by which you say, if that's the kind of case that motivates one to say that there is a need for re-consent all the time, that there's an alternative way of dealing with it. I'm not arguing anything, I'm just --

DR. MIIKE: No, no. I understand.

MR. HOLTZMAN: How do we think about this, how do we respond to a certain line of thinking. What Rachel is pointing to is that maybe we're very indirect -- where there at least loud voices with different positions.

DR. COX: But, Stephen, these testimonies, there was one in San Francisco. I mean, this depth was never there. In fact, to just put it very crudely,

people's view is, listen, you know, I'm not an idiot, so just ask me, I'll think about it, then I'll give you my consent. But to really go into, well, what does it mean to give consent, I don't think that anybody thought about that very deeply. So to think that the people have great insight into that, I think, would be a mistake.

DR. WELLS: Certainly, the groups didn't speak to that sort of issue directly, and we did not present them with scenarios of harms that could happen, but it, in fact, invited them to think about those. I don't think it's very far from anyone's consciousness, Nazi experimentation, or something. But, in fact, other than a couple of obvious examples, like the stigmatization questions, those sorts of concerns didn't loom large in their minds.

I mean, we didn't get people saying, even though when asked how they trusted people to protect their medical information and so forth, they could have presented a lot of sort of dire scenarios. They did, in fact, say we don't trust anyone, at least generically or categorically. On the other hand, they

never expressed the fear of things going that far.

MS. HYATT KNORR: Overall, I was rather surprised at the positive outlook on research.

DR. WELLS: Yes.

MS. HYATT KNORR: I mean, there were a couple of individuals who were aware of things that had gone wrong in the past and mentioned them, but I was really surprised that, even though nobody trusted the government, research was a great thing because it took place at universities.

DR. COX: Again, there are two explanations for this. Either that people really are very deep in this and that they are optimistic, or what many who would argue just the opposite of really open-ended consent forms, the really detailed consent forms, they'd say that people are just naive about this and if they knew more about it, then they would want more.

So I don't think we have enough information, or we have probed deeply enough, to know which of those is the case. I completely agree that the response was a optimistic one, but whether that was because people were optimistic with full knowledge or optimistic --

MS. HYATT KNORR: I would say optimistic and naive.

DR. EMANUEL: It's optimistic, and that's what our culture says. We have a big belief in progress and science. When you ask for their gut reaction, that's what their gut reaction is. It's no surprise.

DR. WELLS: No one really challenged the notion that the research itself would result in a good.

MR. SIMON: But these are also folks that, a half hour before we got to this level of discussion, started off saying that they thought this was all dumped material, so why would they possibly be concerned if it's kept anonymously to work with? So there's that to keep in mind, and that would put forward the assumption that it was naive optimism.

CHAIRMAN MURRAY: I have to ask a question right now. Is there any member of the audience here who wishes to give public testimony?

(No response)

CHAIRMAN MURRAY: We're about 20 minutes behind schedule, but we have 30 minutes built in at the end of the morning. So I think we can go a couple of

more minutes on this subject, but then we should take our 15-minute break and then resume.

DR. WELLS: In response to what Sean said, and in thinking about a survey, one of the drawbacks of a survey is that if people's opinions are not already well-formed, that the survey is not an ideal tool for getting at unformed opinions. So, to the degree that we are sort of using the questionnaire not only to elicit their responses but to sort of preload the conditions under which we're asking them to form an opinion, it's going to be more problematic.

In fact, you're more likely to get standard expressions of values, which I think is what we did with research in these groups. So we should keep that in mind as we're going into a survey, is the fact that people have no idea that tissue is even stored, is a potential drawback.

DR. EMANUEL: I absolutely agree with you, and I think it's a big problem and one of the reasons we decided not to go ahead with a big survey. So I think anytime you would interpret these kinds of survey data, you would go with a big grain of salt.

On the other hand, now that we've gone through the focus groups, we do find some themes, and it's important, I think, at this point for us to know, how robust are those themes, and how biased. I agree, this is the worst area to do surveys on, because there's no public discussion. They don't even have the foggiest idea of what's happening. Yet we want to get very specific, and we have all of these hypothetical problems. On the other hand, there are at least several key questions which I think would be helpful if you could develop some good questions.

DR. MIIKE: My question to Zeke becomes more important because, and Dave said it exactly, and that is, in your work on this commission are you coming in from your research? I need all the information before I make a decision -- coming in from a public policy decision. That's the information that's out there and that's what I've got to rely on to make that decision.

DR. EMANUEL: But I'm not trying to --

(Laughter)

DR. MIIKE: I hear a hesitancy to move forward on the policy --

DR. EMANUEL: Oh, not at all. Not at all. I'm always willing to give my attention to policy recommendations.

CHAIRMAN MURRAY: Who needs stats?

(Laughter)

DR. EMANUEL: As I started the three previous meetings of this group, those are irrelevant.

CHAIRMAN MURRAY: Jim, you have a couple of minutes where you were going to reflect on the general usefulness of this technique on future commission work.

DR. WELLS: Well, I think I kind of alluded to the fact that, because this is an area where there are a lot of unformed opinions, focus group, meeting, hearing, forum sort of approach, group discussion is a good place to do that.

I mean, clearly there's progression from the beginning of the discussion to the end, where, in some cases, we were able to elicit some pretty sophisticated and thoughtful ideas about these issues. I think to get at these things if we just walked up to somebody and said, what do you think about informed consent for linked studies on tissue, they would give you a blank

stare.

This is a potential weakness, I suppose, in the sense that you need to get people to volunteer to do this. Not that you don't for a survey or any other information-gathering technique, but, in fact, I suppose we'd have to admit that maybe the most privacy, the people with the most fundamental privacy issues may not have been concerned to talk about somebody on behalf of a federal commission about these issues. I don't know.

I don't know that that's the case, but there's some selection bias in every opinion-gathering technique. So that's potentially a drawback. Nevertheless, I think the people that came in were willing to be open and to openly share their opinions and to, in fact, divulge those opinions to others in the group and to allow that interaction to occur. I think that's fundamentally the strength. The fact is, we didn't know precisely what to ask or how to ask it, and that evolved over the course as well.

CHAIRMAN MURRAY: Any final word? That was a good summation.

DR. WELLS: I guess not. That was the final word, on the technique.

CHAIRMAN MURRAY: Thank you very much, Dr. James Wells.

MS. KRAMER: This was invaluable.

CHAIRMAN MURRAY: We're going to take a 15-minute break, which would have us back here at 10 minutes to 10:00. We will start promptly at 10 minutes to 10:00, and Sheri Alpert will lead off.

(Whereupon, at 9:40 a.m., the hearing was recessed.)

AFTER RECESS

(9:55 a.m.)

CHAIRMAN MURRAY: Let's reconvene.

Sheri Alpert is going to make a very brief report on the paper she's done for us and the work she's done for us, and there will be some time for questions and discussion.

Sheri?

PRIVACY AND THE GENETIC ANALYSIS

OF STORED TISSUE: UPDATE

By Ms. Sheri Alpert

MS. ALPERT: Okay. I'm making a presumption that everyone's had a chance to read my paper and has had a chance also to look at the conclusions and recommendations, but I'll quickly go over what those are, since those got out a little bit later than the rest of the paper did. These are just highlights.

There were basically four areas that I found

that were the most useful for looking at conclusions or policy recommendations. One, is the issue of groups, which you've already been discussing quite a bit. The other, I called Other Genetic Research because I wasn't any more creative than that. One is protecting anonymity, and then finally, tangible and intangible harms.

The nature of my recommendations are fairly explicit as far as policy recommendations within the context of the regulations to protect human subjects, in some cases, not all.

So the first one that I thought was important is that the regulations to protect human subjects should explicitly incorporate a notion of non-medical group risks and harms that is possible by participating in genetic research.

Right now, the regulations don't really acknowledge any kind of harm beyond the individual, first of all, and second, don't really incorporate the notion of a non-medical risk or a non-medical harm that might be a possibility.

CHAIRMAN MURRAY: There's a question.

MS. ALPERT: I'm sorry. Yes?

MR. HOLTZMAN: With respect to non-medical harms, it may not be in the regulation, but someone help me here, there was a specific directive probably back in 1994 that one had to take into account of those non-medical harms and it was specifically in the context of genetic studies that that was raised. Correct on that?

MS. ALPERT: I'm not -- I don't know for sure.

MR. HOLTZMAN: It is. I know that for sure.

MS. ALPERT: Okay.

MR. HOLTZMAN: I don't have the reference, but you should find that out, or I can find that out.

MS. ALPERT: Okay. But I'm also explicitly saying that it should be incorporated into the regulations.

MR. HOLTZMAN: And then the second thing I would say with respect to, as we think this through, and you don't want me to keep raising this, whether the word "genetic" is important in that first recommendation.

MS. ALPERT: Right. Okay. And I guess I

should point out at this point, when I talk about genetic research, as far as groups are concerned, I am thinking in terms of research that's been done to come up with BRCA-I, BRCA-II, Tay-Sachs, the colo-rectal cancer mutation, where you know what group you're dealing with when you start dealing with that group.

That was what I had in mind when I was addressing this issue.

And also, my definition of groups is -- I mean, there are several ways to cut it. The cut that I'm looking at here is ethnic, racial, cultural kinds of groupings as opposed to necessarily just disease groups or geographic groups. So, okay.

Second, tissue samples from which group affiliation is known or can be inferred, however it can be inferred, for the sake of the regulation should not be considered anonymous tissues for research because you know, especially if those tissues are being used to further research on that particular group.

So whether or not they're individually identifiable to a person, if you know that that person is a member of a group that you're interested in

studying those tissues, I'm saying, are not anonymous and should not be treated within the regulatory process, within the IRB process, as anonymous.

MR. HOLTZMAN: This goes to something we've been talking about, that the salient point is whether the tissue in the relevant sample is anonymous or the study of the taking with the tissue.

MS. ALPERT: I'm sorry. I couldn't hear you.

MR. HOLTZMAN: Is the issue the state of the tissue or the nature of the study undertaken with the tissue?

MS. ALPERT: The nature of the study undertaken.

MR. HOLTZMAN: Okay.

MS. ALPERT: Third, were group research is proposed, and this is consistent with the model protocol, for instance, from the Human Genome Diversity Project, where group researchers, proposed researchers, should involve leaders of the relevant groups and communities throughout the entire process, whether it's research design, recruiting participants or research subjects, and potentially the communication of the

research results. That, to me, is fairly important.

Moving on to Other Genetic Research. The first ones, I know, are going to be really controversial. The more identifiable the subject is in the context of genetic research, the more important it is to obtain informed consent, even on retrospective or already existing tissues and data.

If the tissues and data are being used anonymously, it's not as much of a problem, not looking at the group issues, I'm putting those aside. This is somewhat consistent with what Eleanor Clayton has written, and others, although I think this backs off a little bit from that.

But, again, the more identifiable the tissues, the more important it is to try to obtain the informed consent of that individual.

The second one, and this kind of gets to some of the questions or the issues that were being raised just before the break, issues of consent. In clinical situations where patients are asked to provide consent for their tissues to be used, that it shouldn't necessarily be a yes/no.

There is a range of choices that could be offered, and should be offered, to individuals in the context of whatever research might be done on their tissues. For instance, there are two separate ways I'm cutting this.

One, is for prospective collection, anonymous, unspecified use in the future, the range could go everywhere from I do not consent to the use of my tissues for any purpose whatever, to consent to any type of research. But, again, keep in mind, I'm talking anonymous here.

The two in between would be consent to research on my disease only, or beyond that, perhaps, if that does not include genetic research, then genetic research is okay as a third option. That's consistent, I think, with the National Action Plan on Breast Cancer, the direction they were going.

DR. EMANUEL: Can I just mention something here. Over the -- I guess on Friday or Saturday I actually tried to think and draw up a prospective opt-out sheet, and I can actually distribute it if people are interested. But this turns out to be actually much

more difficult than one might think sitting here. Let me suggest why.

First of all, the National Action Coalition--and I always butcher the name and I'm not even going to try anymore--were specifically focused in on women with breast cancer, so they had two advantages: women who were having biopsies for breast cancer, and cancer.

If we are going to do a general form, you don't have those two grounding points, it is much harder to write an open-ended form that way. So, for example, the second one, consent to research on my disease.

Now, imagine you're going in for a biopsy of your breast. Since 60 to 70 percent of those are benign, what is my disease? There isn't a disease there, and it becomes immediately problematic. You're trying to imagine or trying to propel something.

The second thing, is my solution to this problem was a two-step solution. That makes a consent form difficult to do without someone there. You have two sets of questions, actually, to ask, not one set.

So I think it actually turns out to be a very

useful exercise for us to think about actually practically implementing this because the recommendations that I was pushing may not be as easy to do as people may imagine, and spending an hour sitting in your room trying to write out something may give us a flavor for some of the difficulties and problematics with doing it.

DR. COX: Not to mention the quizzical looks on the faces of the people who are trying to do it.

DR. EMANUEL: Well, just think about it. If you don't do it in person with someone where you can actually ask a question, okay, because we don't want to do it right before surgery and we don't want to do it right after surgery, it's a serious, serious problem. Maybe if people are interested, I can show them some of the things I came up with. But, anyway.

MR. HOLTZMAN: I forget her name, the woman from Canada. Implementation was of presumed consent or opt out.

DR. EMANUEL: She was talking about the Netherlands, that was beginning to have an opt-out system.

MR. HOLTZMAN: Did we see what that looked like?

DR. EMANUEL: No. I mean, I'm sure we could get it.

MS. ALPERT: Okay. This was just one possible take on --

DR. EMANUEL: No, no. We've all been talking about it.

MS. ALPERT: Number two, another way to cut this, potentially, is to have the range of consent vary around the identifiability issue so that you would either not consent at all, and I apologize for not putting that one on there, you would consent to donate anonymously, consent to donate only where a tissue bank trustee knows who you are, and then a further consent within that consent is, I agree to let other researchers who will not know who I am go back to the tissue bank, which can then contact me for further information, if that be the case.

In that case, if that is what a person consents to, they will not receive information back on what the results of the research may have found.

The last one then is consent to donating tissues with full identifiability, with the catch being that whenever the tissues and the information go out to a researcher, before that researcher can use that collection, the data, the tissue, et cetera, they would have to come back to you as the tissue source, as the tissue donor, to get specific consent for a specific protocol. Obviously, this is prospective.

Again, the question was raised, I think Steve raised it, whether or not someone can give an informed consent for general purposes when you don't know what the harms are and you don't know what the actual research is going to be. Giving an open-ended consent like that is really not informed, or not necessarily.

Moving on then to protecting anonymity. This is also consistent with where discussions have been going. A fire wall should be considered between the researcher and the repository, or the tissue collections. I'm saying for both retrospective and prospective. They're already existing in prospective.

One of the main difficulties is going to be defining exactly who falls on which side of the fire

wall, because there are a lot of pathologists out there who do research on their own collections, and you have to figure out where they would fall within that, on which side of the fire wall they would fall.

Just a hunch, that's probably where most of the research, or a lot of the research, anyway, is being done, in that kind of a context, where the pathologist can sell them -- research, not necessarily in the context of the protocol.

DR. EISEMAN: I wouldn't say that most research --

MS. ALPERT: Well, a lot of it.

CHAIRMAN MURRAY: No. Some of it. Very little of it, from what we hear from the expert on pathology.

MS. ALPERT: Okay. All right.

DR. EISEMAN: I think more samples come through pathology that are passed on to other researchers --

MS. ALPERT: Right.

DR. EISEMAN: -- but not necessarily -- the pathologists themselves.

MS. ALPERT: Okay. All right. Okay.

Well, leaving pathologists aside, it's still important to know who's on what side of the fire wall and how that fire wall will be constructed. I think I laid out in my paper a couple of different ways, that it could be either an institutional arrangement within the institution, it could be a trusted third party to use prevalence of the encryption world, where an outside or totally independent board or body would be the tissue trustee.

Then, finally, tangible and intangible harms. This is kind of motherhood and apple pie, I suppose, that the research and policy communities need to be vigilant in trying to minimize harms and risks.

Again, I say genetic research in a context of assuming that that is going to elicit more information that is sensitive to the individual than might otherwise be from other kinds of research.

I'm saying that part of that vigilance needs to be a sensitivity on the part of the research community and how research results are communicated to the public, because I think to some extent that may be

part of the issue of what may scare people about the possibility of participating in genetic research.

I suspect that's part of the back lash that has been experienced in the Ashkenazi Jewish community, where some of the community leaders are trying to pull back on the conduct of research on Ashkenazi Jews. Like, pick on somebody else; you've done us for a while now. It's someone else's turn.

So if the research results were, or could be -- and I'm not even suggesting how because I don't know, necessarily. But to the extent that the findings could be communicated in a way that doesn't scare the public, that would really be helpful in the conduct of future research and genetic research.

DR. EMANUEL: Can you pop the first slide back up? I think it's your second point there that struck me as quite controversial. That has not been the drift of our discussion at all. We have tried to reduce the number of categories from either anonymous or identifiable and not to have a spectrum of kinds of anonymous or kinds of identifiable, then within each of those categories, thinking about subclassifications.

The general view has been that, if the tissue sample is handled in an anonymous manner where the anonymous refers to the individual identity, then it's being considered anonymous. I mean, that's been our --

MS. ALPERT: But there would be an individual in the group as well, right?

MR. HOLTZMAN: It was probably after this point, but if you read the second point, there's not a reference to the state of the tissue, but rather the nature of the research.

MS. ALPERT: Of the research, right.

MR. HOLTZMAN: And I'm reading point two to be nothing more that a study could be anonymous with respect to the individuals but not anonymous with respect to the group. We have called out that.

MS. ALPERT: Right. And I'm talking about the nature of research.

DR. EMANUEL: Sorry. But if you go back to the revised slide, right, this is anonymous identifiable.

MS. ALPERT: But where I'm talking about is, I'm looking down here.

DR. EMANUEL: All right. But this is the use of the tissue, or what we had considered the use of the tissue. Within this classification, because that said whether it was done for a group. Okay.

Maybe I just misunderstood. I thought you were saying anything in this category, this should be a blank and it should be shifted over here, is essentially the way I interpreted that.

MS. ALPERT: If the research is only this entity and you know it's only on that entity, I think you're probably right.

DR. MIIKE: Maybe the answer here is how we're discussing this. Put Sheri's slide back up. The confusion here is the use of the words "tissue samples" and all of the discussion we have about anonymous, anonymize, et cetera.

What you're basically saying here is that we should treat groups differently. That's all you're saying, I think. So it should not be framed this way. It's sort of like your overall point that there are issues when identifiable groups are involved in the research. So I think the way that it's stated is

what's misleading.

DR. EMANUEL: I'm not sure I agree, and here's the reason. Remember, that's true for the issue of consent. But let's switch to the issue of IRB approval. Okay. Part of what we had said on IRB approval is that we would distinguish these two. Okay.

DR. MIIKE: Yes. But you see, it says individual, no community linkage.

DR. EMANUEL: Sorry. Let me just get one of the slides where I fill in.

MR. HOLTZMAN: Zeke, your problem is, and I thought about this after the last meeting, is that our X and Y axes actually have certain of the same information.

DR. EMANUEL: Well --

MR. HOLTZMAN: That is correct.

DR. EMANUEL: Look at this for a second. On the individual consent, right here, there are differences in both the IRB review and the level of individual consent we're going to use. So it doesn't seem to me fair to say that we're going to make this -- it might be fair to say that.

It may be what we want to go to. We're going to make this a blank and treat it as if it were identifiable because it has many different implications, at least our last conversation, for the kind of IRB reviews you're going to have, the kind of consent. Remember, if you're treating it as identifiable you've got to go back to the individuals and get their formal consent.

MR. HOLTZMAN: Maybe you're reading too much into that.

DR. EMANUEL: Maybe.

MR. HOLTZMAN: There's a notion of identifiability which we're acknowledging in your conceptual schema, which says community identifiable.

DR. EMANUEL: That's here, right?

MR. HOLTZMAN: Right. Okay. And that's all I'm reading Sheri's second point to say, is that current regulation focuses on identifiability in the context of an individual and an individual only. All right. This commission is acknowledging that there is a sense of identifiability which can exist even in the absence of individual identifiability.

DR. MIIKE: I just want to say, the discussion is getting confused because she's using terms that you're using differently. I'm just saying that Sheri's presentation should not state it the way it is right now, because it just gets the two sides confused.

DR. EMANUEL: Okay, fine. I just think we haven't used the issue of identifiability to refer to communities in our previous discussion, in part, because I think it had different implications for informed consent, among other things, in IRB reviews.

CHAIRMAN MURRAY: Bette?

MS. KRAMER: First of all, can you put your slide back up, Sheri? It's also jumping ahead to whether or not we really demand consent from the group, which we really haven't discussed. I'd like to go back to this. You're focusing on dealing with the group, to what extent? I mean, you've left that very vague, but there seems to be something implicit in it.

MS. ALPERT: I'm not sure I understand the question.

MS. KRAMER: All right. You said, where group research is proposed, researchers should involve

leaders from within the group -- the research is being done.

MS. ALPERT: Right.

MS. KRAMER: Now, are you envisioning that they would have a veto?

MS. ALPERT: In the context of the Human Genome Diversity Project, they do. The question is whether or not you want to go that far. I doubt that you would, and it's not necessarily appropriate to. But the main point of that is that they should just be involved with the process, and perhaps the process of the research design will change as a result of having those groups involved.

DR. COX: I really, again, think that the sort of trying to talk in specifics is important, and that's one of the things that you just did a second ago. So if you're talking about a tribe of people, in the context of the Human Genome Diversity Program and someplace in the Amazon, it's a very different issue --

MS. ALPERT: Absolutely. Ashkenazi Jews in the United States.

DR. COX: -- than talking about informed

consents. Yes. Ashkenazi Jews or some socially defined group in the United States.

MS. ALPERT: Yes. Yes.

DR. COX: Because we're talking about groups here very generically, right?

MS. ALPERT: All right. Again, the way I'm defining groups right here is not necessarily a social group or a disease group, necessarily, but an ethnic, racial, or cultural.

DR. COX: Why?

MS. ALPERT: Well, that's a valid question. Because --

DR. EMANUEL: For at least some of this genetic research, they're likely to be the ones singled out.

MS. ALPERT: Right.

DR. COX: But I would argue that most of the reason for singling out groups are for social and cultural reasons, not for genetic reasons at all. In fact, for figuring out whether groups have genetic components, those groups are picked socially and culturally, not genetically. So, I mean, this is a

very tricky business. We're implying that it has a biologic or genetic basis to the group. And I will tell you, just from the pure science part of it, it doesn't. It doesn't.

DR. HANNA: But I think you have to remember that -- I mean, here's something you can borrow from, the insurance industry. They use group analysis to determine risk.

DR. COX: Bingo. I completely agree with that. But those are going to be group analyses that are based on social and cultural prejudices most of the time rather than on the basis of scientific information. That's the only point that I'm making.

DR. HANNA: I think the connection with people's fears about discrimination are tied -- they're linked right now. Until they're unlinked, I think that that's why there's a tendency for people to think in this group way, because when insurance companies do underwriting, your age, your race, your ethnicity.

DR. COX: Kathi, I'm not saying they're not going to be thinking in these group ways, but I'm saying it's going to be much broader than we're even

defining it right here. Religious groups. That's why I think it's not very useful to think of this in the context of tribal ethnic groups because --

MS. ALPERT: Maybe the Human Genome Diversity Project was not a good example to use then, because obviously in the United States that's going to be more difficult, unless you're doing Native American groups and other indigenous populations in the United States.

I fully recognize that trying to find a community leader in the Irish American community is going to be next to impossible.

MR. HOLTZMAN: Except in Boston.

(Laughter)

MS. ALPERT: You'll find a lot of them?

DR. COX: It won't be impossible, because you'll have self-appointed leaders.

MS. ALPERT: Right. Well, yes.

DR. MIIKE: There's a threshold question here. Has the research been firm on the basis of, let's go look at this ethnic group?

MS. ALPERT: Sometimes it is.

DR. MIIKE: But that's what I'm saying.

That's why these terms are too general, in the sense that you take a small community or we have an Indian tribe, or you have an ethnic group. Now, the former, you can have people who are legitimized leaders that can speak for them. The others, you don't.

MS. ALPERT: Right.

DR. MIIKE: So another consideration is that -- - research project that happens to end up in a particular -- among research subjects that you can identify with a particular characteristic or grouping or whatever, or do you pick a group and then you do the research? So how you deal with these recommendations depend on how you ended up in the project, so there are at least those two there. One, is that if you decide you want to look at Ashkenazi Jewish women and because, for certain reasons, like the breast cancer kinds of studies, it was convenient to pick them, that raises different issues than you sort of do -- you start a research project and you say, oh, look what happened, there's a whole predominance of Irish Americans in here. Then the second level of that is, given that and your concern about group kinds of things, how are you

going to deal with the issue about consent or participation in the research design, et cetera?

Because didn't we hear about in the Jewish women's studies that your Boston people said no, the San Francisco said yes? Now, who's to win? If you do the research in San Francisco, will it have the same implication as Boston?

MS. ALPERT: Yes. What I was getting at was your first point, where you know up front that the protocol is looking at a specific group.

Now, again, this recommendation we put up here is out of context of the rest of the discussion, where, as I said, what I was dealing with was more the ethnic, racial, cultural kinds of groupings of individuals.

You wanted to say something else?

DR. MIIKE: Yes, but not related to what we're talking about. What do you mean by non-medical group risks or harms?

MS. ALPERT: Stigmatization.

DR. MIIKE: So it's a tautology in the sense that just by -- it's not a harm, per se, but it's in the application of the research there is harm.

MS. ALPERT: It's --

DR. MIIKE: You see what I'm getting at?

MS. ALPERT: Yes.

DR. MIIKE: Well, there really isn't any harm. But just the fact that they are now a group that is in the research protocol, it's never an issue about, okay, we happen to be in a group that's ethnically identified in this particular research protocol and the research results end up in a possible stigmatization.

DR. COX: Rich versus poor. You look at poor people versus rich people. Now, does that have anything to do with genetics? There's a lot of people that would say it does.

MR. HOLTZMAN: If your parents had a lot of money.

(Laughter)

DR. COX: You've got green genes.

MR. HOLTZMAN: If you go at a very simple level in number one, and this comes back to what I think PRR, whatever it is, issued as a directive, is that in certain kinds of research there are contemplatable harms which are non-medical.

For example, you might discover something about the status of paternity in a study, not directly to finding that out. Therefore, it raised the bar on the nature of the kind of consent that one needed to -- whether or not this section was in play. So that has nothing to do with groups. I don't think we should confuse those issues.

CHAIRMAN MURRAY: There is a group, sort of non-medical harm, that is very plausible.

MR. HOLTZMAN: But that comes to, I think, again --

CHAIRMAN MURRAY: Having nothing to do with disease. I mean, having to do with the genetics of various behaviors and other things.

DR. MIIKE: But, you see, this is listed there where there are three, and it's under the heading "Group."

MR. HOLTZMAN: I think that's --

DR. MIIKE: That's what I was getting at. Your example is not a group kind of thing.

CHAIRMAN MURRAY: Right. I'm talking about a group situation where you're looking at personality

attributes, propensities towards violence, social behavior, the sorts of things that some people are studying. Not medical, but can clearly come back and sting the group that is being studied.

MR. HOLTZMAN: So why don't we just conceptualized it this way. Forget group versus individual for the moment. Do we agree with the OPRR that there are non-medical harms which arise from the study, and, if that is the case, that the sort of bar gets raised on the study? I think that's clearly the case.

Then I believe this committee has also said that the notion of community linkage can exist in the absence of individual identifiability. We haven't quite figured out what community and group may be, but that we can certainly think of cases where that is paradigmatically true and that, if that's the case, that it's a salient consideration in the nature as a consideration that has to be taken into account. You don't disagree with that, do you?

DR. MIIKE: I don't disagree with that. It's in the details.

MR. HOLTZMAN: And now we're going to have to play it out in the details. All right. So there's an objection, maybe in point three, is that maybe it depends on how much you want to leave it to Sheri's -- around the word "group" as to what follows from it. I mean, she's putting in a robust kind of group consent process.

DR. EMANUEL: It's worth people knowing, the new FDA guidelines about no informed consent research related to emergencies. The FDA has required that the community be consulted and participate. Now, in a sense, everyone is scurrying for, well, what does that mean? Is that the catchman area for our emergency room, is it depending upon the research, et cetera?

So it's a serious problem, but it's not unique, as it were, to us. I think there is this tension, this undeveloped situation, where we recognize things that we're doing have an impact on the community. We have difficulties defining the community. Nonetheless, we feel some obligation to go out and consult with them, even get their consent, whatever the phrase is.

But I'll put it this way. The FDA felt comfortable enough to put it right in their regulations and require it before this research could go forward without going through the levels of specification of exactly who's going to qualify, leaving a lot of that, frankly, to the IRBs to decide. But maybe that's a second order issue.

CHAIRMAN MURRAY: Let me make a suggestion. For many reasons, I'm sorry that Bernie Lo isn't here, but especially because Bernie has taken a particular interest in the issue of group consent.

He's talked about his experience and the experience of other people with whom he works in working towards community assistance, consent, and research, I think primarily in HIV.

But Bernie has some, I think, very rich ideas about how to think about this issue, and even some practical steps that one might take. I'm reluctant to spin our wheels on it in his absence, and I presume he'll be with us in December.

As far as we know, I think he'll be here in December. Well, I will twist his arm to be here in

December. But I'm just going to propose that, rather than get hung up on the group issue today, we try to hold off on that and tackle it full force in December when he can be here. Is that all right?

DR. EMANUEL: Good idea.

MS. KRAMER: Tom, in his communication he indicated that where he thought the benefit of interacting with a group was, it seemed to me, this is the way I read it, was in fleshing out the research protocol in increasing or refining the number of participants, but not in giving them any veto over the research, not in actually requiring or allowing them to give an informed consent. It was more informal.

CHAIRMAN MURRAY: Well, I think we need to have Bernie here to develop further these thoughts on that. I would be reluctant to speak for him.

MS. ALPERT: Can I just say one thing.

DR. GREIDER: I want to raise a totally unrelated issue, but it has to do with the thing you just took off. We're not done discussing this, right?

MS. ALPERT: I'll put that back up. I'm not necessarily suggesting that groups have veto power,

but, to the extent that whatever community involvement can be obtained, that the results of that go into an informed consent for the individuals who are going to be consenting for any kind of a prospective research protocol so they can evaluate for themselves whether they want to participate.

CHAIRMAN MURRAY: Maybe you've opened the possibility of effectively a community veto over retrospective research. We just have to think those things through, and I just feel like we'll do a better job with Bernie Lo sitting with us.

MS. ALPERT: I just wanted to say that.

DR. GREIDER: I just wanted to raise a somewhat unrelated issue, and it gets to the heart of the fact that the first recommendation you put up there ends in "participating in genetic research." It's taken as a presumption in what you've written here that genetic research is no different than other research.

MS. ALPERT: Right.

DR. GREIDER: And I just want to raise for this committee that we need to think about that and discuss it before we have it written into all of the

things sort of explicitly that that is true. So I just want to raise that for us to think about because, personally, I don't necessarily agree with that, and it's implicit through everything that you've written. So we need to consider that explicitly.

DR. EMANUEL: But I thought, actually, a lot of the conclusion from our last meeting was -- and a recognition that that wasn't the case, that lots of these concerns extended way beyond genetics.

DR. GREIDER: But all I'm saying is, everything that she's written, it's explicitly distinct, which I feel like we didn't come to that conclusion. So should we think about it again before we have it sort of seep into the way things are set? I don't know that we explicitly decided anything.

MR. HOLTZMAN: And if we explicitly decide that, we think it's not a useful distinction, we can certainly write that in the body of our report so that it doesn't embody that distinction. We probably need to argue for why it's unimportant, and I think that's in Kathi's outline.

But then the question is, when you publish

your appendices which include the contracting papers, to what extent is one comfortable having papers reflecting that as a conceptual starting point?

DR. EMANUEL: I think the charge to Sheri was to look at the genetic side of it, but I think part of my conscious point of distributing the papers I did last time was to say, look, these issues come up. You're not looking at genetics, you're looking at angiogenesis. You're even just looking at records review. So it's --

CHAIRMAN MURRAY: Do we want to ask Sheri to do what would be, in effect, a pretty light revision, to take out the emphasis on genetics, or do you want to leave it as it stands?

DR. EMANUEL: I don't think it's that light a revision, actually.

CHAIRMAN MURRAY: You don't think it's that light a revision.

DR. GREIDER: Well, and it could be said explicitly that this is about genetic research, and not that it is somehow distinct from other research. But I haven't actually read this second draft.

The first draft that I saw said explicitly that genetic research is different than other kinds of research, and that's not how I felt that we were coming to a conclusion in this commission, so I felt uncomfortable with the way it was previously.

CHAIRMAN MURRAY: I don't recall that.

DR. GREIDER: I certainly do.

DR. EMANUEL: In the first draft, perhaps, I don't recall.

DR. GREIDER: I'm sorry. I haven't gotten to the second one.

CHAIRMAN MURRAY: Would you put a paragraph in, at minimum, Sheri, just explaining that the initial charge was to look at the implications in genetics research, since we're all the Genetics Subcommittee, but that one should not read into that that the issues that we raise are solely --

MS. ALPERT: Okay.

DR. MIIKE: In your original outline, wasn't there supposed to be a section that addressed this issue head-on, about whether genetic research was any different? Wasn't there --

MR. HOLTZMAN: We need that. That's very important, I think.

DR. GREIDER: I mean, we need to discuss that.

MR. HOLTZMAN: That's in Kathi's. It's in our report outline.

DR. MIIKE: No. But I thought it was in Sheri's original proposed paper.

CHAIRMAN MURRAY: Sheri doesn't even remember.

MS. ALPERT: Sheri doesn't remember it.

MR. HOLTZMAN: No. I mean, for example, if you look in Sheri's paper on page 2, the third full paragraph, the sites -- the typical place in the literature about why genetic information is distinctive.

DR. GREIDER: Right. That's why I mean that it's implicit throughout, yes.

CHAIRMAN MURRAY: I would request that you leave open the issue of, and in fact, I think, reflect our intentative conclusion, that genetic research in this context and in these types of uses is not -- there's no clear and bright line between genetic research and other forms of research.

DR. EMANUEL: Yes. You might say that it's paradigmatic or opening our eyes to this, but that we can see it's probably true in lots of other types of research.

CHAIRMAN MURRAY: That's a good way of putting it. Thank you.

Any other questions for Sheri? We are running behind and I do want to get the next paper up here as soon as possible.

(No response)

CHAIRMAN MURRAY: Thank you, Sheri, for your good work on this.

Robert Weir. Thank you for coming in from Iowa.

DR. WEIR: Yes.

## THE ONGOING DEBATE ABOUT STORED TISSUE SAMPLES AND INFORMED CONSENT: UPDATE

By Robert Weir, Ph.D.

DR. WEIR: Well, you have received, as I understand it, the text of the paper that I wrote, so I will simply make some very kind of cursory comments about it, going to just a few parts of it, and then be prepared to discuss it with you.

The first page is an attempt to sort out three sets of issues in the sense of questions. Again, I was commissioned to write a paper having to do with the debate that has developed in our country about the issue that we've been talking about this morning.

Some of the questions have to do with, how specific do consent documents used in research settings need to be regarding the intended purpose of research study in order for research petitioners to get informed consent?

Another cluster of issues really focus around the question, how much information about the possibility of post-diagnostic research on stored tissue samples needs to be given to patients in clinical settings in order for them to give informed consent?

Third, how much can the ethical and legal requirement of informed consent research be expanded and strengthened before this beneficial research is done by geneticists, pathologists, and other researchers is seriously impeded?

In the paper I tried to go through all of the major documents that I know about that have been published, or not published, a number of position papers that have been put forward for our consideration by the American Society of Human Genetics, the American College of Medical Genetics, the College of American Pathologists, the AAMC, the Korn Group, and others, and tried as best as I could to sort out their various claims and kind of see where they agree and where they don't agree.

Then, if you have the text with you, I tried to put in some kind of capsule form on the bottom of page 17, what I see as the issues of competing bounds in this debate.

I say, in its simplest form this is a debate between, on the one hand, professional groups and individuals who think that in the era of molecular

genetics, increased emphasis needs to be placed on the distinctive importance of personal and familial genetic information, the right of personal choice about the use of one's body and the tissues taken from it, and the necessity of being able to exercise a measure of control over that research, over the research that can be done with one's tissues.

On the other hand, professional groups and individuals who think that in an era of ever-increasing professional and legal regulations, renewed emphasis needs to be placed on the invaluable, and ultimately replaceable, research resource represented by stored tissue samples, the societal and individual benefits that can be gained by means of this research, and the serious threat posed to the continuation of these research efforts by unnecessarily restrictive policy proposals and legislative bills.

Now, after describing what has happened in the literature, I provided a couple of examples having to do with research on stored tissue samples, one of them having to do with neonatal blood spots and the other one having to do with research that has been done with

Native Americans.

The next section then sorts out several policy alternatives--this begins on page 22--which include at least some groups which seem to me to have taken public positions that basically are arguments to retain as many traditional research practices as possible without doing very much to strengthen informed consent considerations.

A second possible solution is to come up with new professional society guidelines, and so some of the groups have tried to do that.

A third possible solution that at least certain parts of the NIH have tried to do is to come up with consensus conferences or consensus meetings where competing groups can perhaps come up with a measure of agreement. One can debate how well these consensus conferences work.

A fourth possible solution is to recommend changes in the Federal regulations and IRB review practices. Some of the documents do this, or at least make these recommendations.

A fifth possible solution is simply to produce

better consent forms.

The sixth possible solution is to mandate changes by law.

Then I got to the point of simply tossing the ball into your court and having the kind of interesting experience of saying, well, you folks ought to do all of these other things because I don't have the time to do them right now, or the resources, so I threw a number of balls in your court.

I won't go through those, except to say that fortunately, at least the first one on page 30 that talks about the need for more data, clearly you're doing that. You're going to come up with some numbers that I sort of didn't know that I think would be extremely helpful to help us get a handle on at least the size of the storage of tissue samples.

Then I basically closed off by suggesting a couple of things, it seems to me, that the operative, substantive principle should be to use reasonable person standards for informed consent and to see where that gets us on this debate, and also to urge some practical kinds of steps to be taken by institutions in

which stored tissue samples exist, including hospitals, to at least apprise patients that post-diagnostic research on their tissue samples is a possibility and, perhaps depending how specific different institutions are going to go, giving them some choice or say in how that research might be done.

I tried to cover a lot of the waterfront very quickly. I hope that the analysis seems to you to be careful, accurate, and reasonable. I tried very deliberately, as I do in a lot of the work that I do, to try to carve out some kind of middle-of-the-road position. We can talk about whether I did that or not, or whether you should do that or not. So --

CHAIRMAN MURRAY: Questions?

DR. MIIKE: Well, one thing that jumped out at me, and I don't see the justification so I'm curious about it, is on page 31 where you call for the discontinuation of anonymizing stored samples without the consent of the person. What is the issue you're trying to address with that, and why did you come up with that specific recommendation?

DR. WEIR: Well, because that seemed -- I was

a participant in that first consensus conference on this issue back in July of 1994, and that seemed to be a major bone of contention among the people gathered in that group. It seemed to be the point at which some of the geneticists at that conference said, we may agree with a lot of other of your recommendations, but we can't agree to that one.

DR. MIIKE: No, no. That's fine. But I want to know what the problem is that you're trying to address with this particular solution.

DR. WEIR: Well, the problem I'm trying to address is the practice that seems to me to be fairly common, at least in certain research areas, of taking samples and anonymizing them and doing it in such a way as to suggest that there is absolutely no ethical problem in doing this, that nobody cares, that it doesn't matter to anybody.

And I have been at least curious enough about this among other issues here that I've done a few pilot studies, surveys, in connection with the grant proposal that I have pending, to try to find out if this bothers -- I mean, if this is kind of a theoretical problem

that only academics like me worry about, or if it's a real problem with real people.

DR. MIIKE: But I think it's a real problem and you're worried about that nobody cares about it. I still don't know why this is the solution, to get consent from the person. To say that, I consent to anonymizing, why that particular solution to that problem?

DR. WEIR: Because it gives the person for whom the tissue sample comes a vote or a say in that rather than simply doing it automatically without giving that person the kind of say.

DR. MIIKE: Is your proposal then that at the time the anonymization may occur, that they're to be asked, or at the time that they give the tissue --

DR. WEIR: Yes, the latter.

DR. MIIKE: So it would be just within a range of kinds of things to say, this may happen to your tissue.

DR. WEIR: Yes.

MR. HOLTZMAN: Can I ask for a clarification?

DR. WEIR: Certainly.

MR. HOLTZMAN: Are you talking about an irretrievable, irreparable anonymization of the sample, and that is where you were saying that that only ought to take place with consent, or are you saying that it's with respect to uses of the tissue in an anonymous fashion?

The reason I'm asking that question is, it seems to me that there's sometimes a systematic confusion, again, between, are we talking about the sample or the research.

Many people have argued that, while some people say just anonymize the tissue and therefore everything will go forward, others have argued against that as being problematic because you can't do the epidemiological work of adding information. On the other hand, it makes it impossible to go back and have the personal, individualized benefit. So I'm asking, what was at stake here when you made this recommendation?

DR. WEIR: What I was thinking about when I made that recommendation was the former of your options, that is, anonymizing the sample itself.

MR. HOLTZMAN: So you're not arguing here -- well, let me ask it as a question. Are you arguing here that in the case of a sample which has not been irreparably anonymized, that the individual's consent has to be sought, either up front or downstream, for the use of that sample in an anonymized fashion in research?

DR. WEIR: Could you give me an example of what you're thinking about when you raised the question?

MR. HOLTZMAN: Sure. Zeke's a pathologist. He's got a collection that's tied to the individuals. I'm a genetic researcher. I come to him and say, I'm interested in people with colo-rectal cancer. He passes on the sample to me such that I can't identify who the individual is, or group, for that matter. I'm conducting the research in an anonymized fashion. I publish my results, and it would be impossible to say that Individual 2750 in my study is so and so.

DR. MIIKE: It doesn't matter though, because if you're asking for the consent up front --

MR. HOLTZMAN: But which consent is he asking

for?

DR. WEIR: Well, actually, if I were -- this quickly gets to the problem of the distinctions that I and some other people might think is important, and how much you can actually practically ask people without overwhelming them with --

MR. HOLTZMAN: Well, put aside the pragmatics for a moment. I'm asking the question of which you were recommending here. It's a very simple question.

DR. WEIR: Well, I'm concerned about both of them.

MR. HOLTZMAN: So which are you recommending here, both?

DR. WEIR: I was thinking when I was writing that, I was writing it about the anonymized samples themselves rather than the anonymous research use of the sample.

DR. EMANUEL: I've got two issues. The first, goes back to this divide that you gave us on pages 17 and 18. I read it as Korn vs. Clayton, you know, unvarnished. I find that actually very unhelpful. They do represent polar opposites of the debate, but I

think, maybe for that reason or whatever reason, unhelpful.

It seems to me part of what we need to say is that both sides have quite legitimate and important values at stake, and the way it's polarized is almost as if you have to choose between them. I think that's a very bad way of putting it.

I mean, part of what I think everyone who approaches this should say is, there's a spectrum of values. I mean, if there was only one value at stake it would be relatively simple. But because we have a spectrum of values -- and it's not necessarily that what we're doing is balancing the values. I don't like that metaphor for lots of reasons.

But we have to consider how each of them are played out and realized. So I find that too polarizing. Encouraging people to take a stand without, in some sense, recognizing that they, too, accept the other side, accept the values of the other side.

DR. WEIR: Well, I don't appreciate your characterization. It was not an attempt of mine to

over-simplify the issue and it is not, as you suggest, Korn vs. Clayton. One of the reasons that the one and the two parts of the sentences go on for an awfully long time is an attempt on my part to build in some of the -- values in that statement.

DR. EMANUEL: But you say in the opening of the sentence, "in its simplest form."

DR. WEIR: I think it's a complex issue.

DR. EMANUEL: And it does say one versus two. I mean, that's the way the sentence is structured, right?

DR. WEIR: That's right.

DR. EMANUEL: And one is everything related to consent and control, and two is everything related to research.

CHAIRMAN MURRAY: I did ask Robert to look at how the debate was structured, and I think he was following through with those instructions when he did this. Now, I also agree with you that, if it turns out there is a much richer cast we can give to this effort to sort of deal with the values.

DR. EMANUEL: All right. The second thing I

wanted to go to is, the sense of previously collected samples that we now have and the sense of prospective or samples to be collected after some recommendations are laid out.

I guess I'm not 100 percent clear whether you think that distinction is very valuable or not and whether you think how much what the ideals, which I think is what we would like to recommend for the future, should work backwards into what we already have.

DR. WEIR: I think both. I think the distinction is important. I think that in terms of coming up with policy recommendations in the future, I think at some point, again for reasons of just practicality, we have to acknowledge that there are certain kinds of existing -- all kinds of existing collections for which no informed consent was every given --

DR. EMANUEL: Right.

DR. WEIR: -- but for which it would be silly, if not impossible, to try to re-consent individuals. So it seems to me that we need to place most of our

emphasis upon prospective samples and say that, for the existing samples, we need to do at least two things.

We need to come up with criteria for which we can accurately characterize some collections as existing as opposed to other sorts of things, and even that gets to be an interesting kind of question.

Second, we need to come up with criteria for research access to those collections. But I think most of the emphasis needs to be placed on the prospective.

DR. EMANUEL: That's interesting. I would remind my fellow commissioners that the reason I think this was put high on our agenda is because researchers are now feeling paralyzed about using existing samples. Certainly when I go around talking to and listening to researchers, they feel comfortable putting in a paragraph into their consent forms now that this is what we're going to -- you know, we're going to collect them, we're going to use them for genetics.

But everyone is so, we don't know what to do with the past, and that has created a certain hesitancy -- not a certain, but a large degree of hesitancy about going forward with research. IRBs are not sure whether

it's ethical or not.

So in some sense it's 113 or however many million samples we have out there that is -- you know, everyone is sort of looking at each other about and not doing anything with in a very active, or as active a manner as they might. That actually, if I'm not mistaken, in part, was the motivating factor for us to really take this seriously.

CHAIRMAN MURRAY: Yes. I think that is correct.

DR. EMANUEL: I think we shouldn't lose sight of that.

CHAIRMAN MURRAY: We're not going to.

David?

DR. COX: Yes. I'd like to say that I found this particular paper very, very helpful, for two reasons. One, I look at it as the exact opposite of what you just said, Zeke, is that I think that, unlike any other thing I've seen written down, this is an actual, not a rewriting of history, but it's an actual recounting of history. You can't help it if people wrote polarized papers, but they did. I also find it

not helpful at all, but they exist. I didn't see in your paper a suggestion that we pick one or the other side.

DR. WEIR: No.

DR. COX: But we live in a world today where this is a polarized issue and it didn't happen just falling out of the sky, it happened because people wrote polarized papers. That's point number one. I find the accurate, historical recording of that extremely useful, if anyone actually wants to get an accurate historical recording of it.

The second point, though, which was practically of utility to me, was that I think that all aspects of the issue are encapsulated in your paper. Although it doesn't necessarily give relative weights to those, I found it extremely useful to have all of those aspects incorporated here.

What do I mean by that? The distinction which we talk about here in our group, the distinction between, is it research or clinical, the distinction was the samples taken as part of a medical test that they used for later research, all of these sort of

different components are here.

In fact, it's another basis on which one can make a spread sheet, a chart, like you have done, Zeke. I'm not suggesting we make a new one, but I'm saying that this could be a really good basis for making sure that, in our report, we're at least considering all of the different issues.

I get a feeling in our discussions that we frequently do not. What we do is we get focused in one or another of these areas and then we look at it very intensively, instead of saying, all right, what are the practical issues?

Where are most of the samples, what are the practical issues for those samples, and how do we deal with them given the fact that today we're in a situation where the issues are very polarized by things that people have already written.

So I agree, we're not looking for polarized solutions. But I think to look to this paper as an example -- I'm happy to volunteer to write down what I see this whole broad thing is, to take out of this at least what I see those broad things are.

But I found this an extremely, extremely helpful paper, not so much for the recommendations because I'm still sort of agnostic about exactly what we should do, but making sure that we've got the whole structure in place.

Right now, I think we've got the cart a little bit before the horse because I don't feel very comfortable that we're discussing the whole structure. We're discussing individual pieces, but not in the context of the whole structure and where each piece fits with respect to the other.

CHAIRMAN MURRAY: David, I wonder if other commissioners feel as I do. I'd like to take you up on your offer to write down what you think this is.

DR. COX: It's a deal.

DR. MIIKE: And we can criticize.

DR. COX: My pleasure.

CHAIRMAN MURRAY: Savagely, of course.

DR. COX: I take Zeke to be making a more subtle point, and if it's not Zeke's point, it's my point, without subtlety.

(Laughter)

DR. COX: I think the paper was excellent as a recitation of the debate as it has existed today. I think that that debate, simplified, is well-characterized on pages 17 and 18 and, indeed, well characterizes Clayton vs. David Korn. Okay. I think, therefore, as we go into this it's very important to have all of those categories that people have used in the debate.

But the subtler point, if you will, is to then ask the question, do you want to adopt those terms of the debate? Do you think that that is the most useful way to be thinking about these things? Because what I took as an implicit position here, maybe incorrectly, was, well, we're going to find a middle of the road which takes some of this, and takes some of this, and takes some of this, but, in fact, maybe that's not the right answer. Maybe you're stuck in a way of thinking which is, in fact, not useful.

So I take it, for example, when we come to a conclusion that the distinction between clinically versus non-clinically collected with respect to retrospective samples is irrelevant, maybe that's a

movement forward in the debate. Okay.

Again, I want to point here to the Campbell paper about the range of values on genetic versus non-genetic. We start to say, maybe that's not important. Well, what really was the itch people thought they were trying to scratch using that distinction?

So the second half of what you said was saying, once we've got it laid out, then we'll be able to deal with it. I think we need to go past the way people have talked about this.

CHAIRMAN MURRAY: In some ways, we're prisoners of our metaphors. The middle of the road, David, reminds me of a saying I think I heard in Texas. The only thing you find in the middle of the road is yellow lines and flat armadillos.

(Laughter)

DR. COX: Exactly.

CHAIRMAN MURRAY: And I don't think we want to be there.

DR. COX: I completely agree with you from the point of view that, just because people write extreme situations, that you don't try and sort of make

necessarily lemonade out of it, although we've heard examples in a paper that suggested that that may be a good thing to do. I would say that if we don't have for ourselves what the whole picture is, then we're not in good shape.

MR. HOLTZMAN: I agree with that. All I'm saying is, the whole picture has been articulated against a certain conceptual formula, in which framework it is the whole picture. It may be the wrong picture.

DR. COX: I don't disagree with that. I actually think there's components here that are much broader than anything that's been published. That's why I liked the paper. But I'm just encouraging our genetics group to have a picture. Maybe we do, but I've got the stuff from the last meeting and everything, and if we do, okay, then I'd like somebody to write it down for me because I don't know what it is.

So I'm more than willing to write down what I think the components are that go into it. Kathi, you have an outline for what our report is, but I still

don't know, overall, what the components that I'm sort of trying to put things into context for.

I know what our discussions of individual pieces are, but I just don't feel like I've got my arms around it.

CHAIRMAN MURRAY: Well, we're going to make a real effort to get our arms around it after the joint session, because we have the time really to ourselves to struggle with this.

DR. EMANUEL: Actually, I guess, David, that's what I would -- I'm a little -- I mean, we have a sort of two-month window here before we really want to report, either in good shape or releasable, and I guess my question to you is, I'm not sure what the metaphor, the whole picture, is supposed to refer to because --

DR. COX: Let me be very specific then. All right. Again, this is very reductionist. We have certain types of samples that are stored, right?

DR. EMANUEL: Right.

DR. COX: And we have cross cutting that certain types of issues with respect to consent and ethical issues. I want to know sort of, what are the

practical considerations that I'm applying those ethical issues to?

I don't want to just look at them theoretically, I want to look at them practically. We've had really good -- I mean, I'm not saying I'm not interested in theoretical papers. We've had good theoretical papers. But at the end of the day we're applying what we've learned to that to practical situations.

I want to make sure that we're not missing some of those. It doesn't mean that we have to go through and look at every type of tissue sample that is done, it doesn't mean we have to consider every ethical situation or every consent situation that comes forward, but I want to make sure, what are the big ones?

DR. EMANUEL: David, I guess part of the effort I tried to do last week, successfully or not, and that's for everyone here to do, and part of what I thought the benefit of the conversation was, is we got to some of the useful distinctions. We weren't talking about anonymous tissues, we were talking about

anonymous research or research done in an identifiable manner.

We did actually bring a lot of this down to a practical framework and talk about, you know, it's consent here, IRB review there, and part of the reason for bringing in some of those papers and some of the examples was to give it a very practical spin.

Now, again, maybe in your view that framework, as refined, did not get the whole picture. Maybe we're leaving out some key element.

DR. COX: Or define the whole picture. I'll give you a practical example. Steve just said, maybe it's not useful to think about things being clinical versus non-clinical. Have we decided that?

DR. EMANUEL: Well, part of our discussion last week, we did have a sense that, in the previously collected samples, that distinction was not going to be helpful. That was obviously no final, but that was a tentative.

DR. COX: You see, it's issues like that that are very important to me, not because I have a stake one way or another, but once we decide those. So if

that's something -- it's sort of where we are in the discussion then, the key points like that, because they inform where we go.

So, I mean, it's not taking a vote, but it's saying, if we're there, then a lot of other discussions we don't have to have right now because we're there and it informs what we do further on. I'm at a disadvantage because I wasn't at the last meeting, but I read the transcripts, I got everything, and I don't get a feel for what those points are.

CHAIRMAN MURRAY: Are there other questions of Robert Weir at this time?

(No response)

CHAIRMAN MURRAY: Robert, thank you. I think you've heard, I hope, that your paper has been very useful to us.

DR. WEIR: Oh, sure. Thank you.

CHAIRMAN MURRAY: We really appreciate this.

If I could ask Mark Sobel and Frances Pitlick to join us for the next 25 minutes or so.

ONE-WAY TRANSFER OF TISSUE INFORMATION: COMMENTARY

By Mark Sobel, M.D., Ph.D. and Frances Pitlick, Ph.D.

DR. SOBEL: Fran and I prepared some preliminary flow sheets, which I'll send down on both sides.

CHAIRMAN MURRAY: Mark, for the record, could you just explain what you've done.

DR. SOBEL: Yes. We were asked to really expand and comment on the proposal that Zeke made at the last meeting concerning the one-way track, so in essence we're talking about the opposite, in a sense, of what Dr. Weir just talked about and we are trying to liberalize policies for the use of tissue and anonymization. I have overheads to go with the written material.

So we really want to think about ways in which we could maximize use of this so-called one-way track and we started with certain basic principles which, if you'll see at the bottom, really have been adapted, modified, and sort of expanded on from a paper that

appeared in *The Journal of Investigative Medicine* earlier this year by John Merz, Sankar, Taube, and Livolsi.

The basic principles of this one-way track is, first of all, that it isn't a published interest to facilitate research on human tissues; that linked tissues permit the updating of outcome data and permit follow-up; that the identifiability of a tissue is directly related to the risk of improper disclosure of research data, so we must be concerned about potential risks; that identifiability raises the potential for the misuse of research information in the clinical management of patients; and, therefore, that stringent mechanisms should be in place to prevent the feedback of research information to individuals or medical records, except under informed consent and specific approved policies.

So we start with basically the paradigm that Zeke showed us.

DR. MIIKE: Can I ask you a question?

DR. SOBEL: Sure.

DR. MIIKE: The second to the last issue about misuse of research information in clinical -- can you expand on this?

DR. SOBEL: Yes. That really comes from CLEA, which basically states that tests that are used to determine the management of patients' clinical care should be regulated, performed in certified laboratories, under certified conditions. So that, in essence, the vast majority of research that's conducted in most research laboratories does not meet those criteria. I'm not just talking about genetic research, I'm talking about all sorts of research.

DR. MIIKE: But this thing doesn't capture that. I mean, I read this and I said, what do you mean by that? But you're talking about more like standardization.

DR. EMANUEL: No, no, no. He's talking about release of information that you get in the research center.

DR. SOBEL: I'm talking about the research information from my laboratory when I decide that I'm going to develop some test, and no one else has

reviewed the scientific validity and utility of that test, that that should not wind up in the medical record and some clinician should not use that information to affect their care. That's what that means.

DR. EMANUEL: But the calling of a patient when you get a test result in a research setting.

MR. HOLTZMAN: Absent validity, absent establishment of validity --

DR. COX: But the definition of test validity and utility is very different for clinical validity and utility.

DR. SOBEL: Exactly.

DR. COX: And CLEA certainly doesn't say very much about clinical validity and utility.

DR. SOBEL: No. But the new LC task force on genetic tests does start to address that issue and does bring up the issue of clinical utility, although it states that you might not be able to -- you might want to start using a test before there is a final resolution, but there has to be a continual updating of information to assess clinical utility before it is

generally accepted, before a test would become generally accepted.

MS. LEVINSON: It's an improper rather than --

DR. MIIKE: How is that any different from medical practice? They do that all the time.

DR. SOBEL: That's a very good point and it is a concern.

DR. MIIKE: Sorry for --

CHAIRMAN MURRAY: That was an important concern.

DR. SOBEL: I mean, we just wanted to have target points here for you to consider. But I think it is a very important point that there is a potential for the use of research information in a clinical setting where it is not clear to many of us that that is appropriate in most situations, if at all.

I think it is a true concern, and we are trying to work, as you will see through these flow sheets, on ways for you to consider in which perhaps we can still perform research and get research information out, but it would not directly impact back on the clinical care of the actual patient.

CHAIRMAN MURRAY: Mark, in part because this was a concern that our participants in mini-hearings expressed, they'd want to know if things were discovered in research that would be of relevance to them. It is important to just sort of nail this down provisionally. What I hear are two statements which are not contradictory, but just two different glosses of this.

One, is that we don't want to have information being fed back to the clinical care of patients when that information is, itself, utterly unreliable and of highly ambiguous clinical relevance. So I think we can all agree to that.

The second, and I don't think this is the case, that one would never find in the course of research information would be clinically relevant. In fact, one might find that to be the case.

DR. SOBEL: That's right. So what I'd like to point out is that what we're talking about here is one particular approach that one might use in certain situations that does not exclude the already existing mechanisms in which one would put into one's research

proposal and get specific IRB approval for a stated mechanism by which you might propose that patients do hear about their information, and that would be in a very specific informed consent paradigm in which you would use clinical material in a research laboratory, for example, for a rare genetic test where it's very hard to meet the high criteria that even CLEA would establish, but at least that would be under informed consent, approved situations.

So we're talking about a different paradigm here, what Zeke really started to propose last month, which is that you have your patient or donor of information, you have some sort of health care providing system, and you have a medical record.

We'd like to point out that in the medical record there is a number, a hospital chart number, there could be a surgical pathology number, blood bank number, and that we would like to consider the fact that it's not just the data in the medical record that is written down and the lab tests that are printed out with specific numbers, but the actual tissue samples, the actual blood sample, actually also should be

considered as part of the medical record. So we'd like to make that sacrosanct, and that is the clinical medical record.

Now we want to have a situation in which people want to do research on tissues for the public good, and they're over here. We drew this wall. Some people called it a fire wall, an impermeable wall, or maybe a permeable wall in their instructions.

So various terms have been used. We're using the word guardian here, which comes from various editorials in the pathology community in which the pathologist was called the Guardian of the Wax, for the paraffin block.

The reason we used that term is I think it is, in a sense, a connotation here that the people that hold the tissue really do feel that they are a guardian of it because they are protecting it and it is there for the patients' benefit, and whatever excess is there, that has to be evaluated and judged to see if there is sufficient material for research purposes. You can use any term you want, but we're really talking about minor distinctions and nuances.

That guardian would be, presumably, selecting samples on request of researchers which would probably involve some professional expertise. If it were the pathologist, they would have to have some knowledge of the actual tissue architecture to determine which parts of the block are appropriate for that research study. If it was a clinical specialist of another sort such as the geneticist, they would have to know what blood samples to obtain from the freezer or from their bank.

The guardian would provide a research code. In other words, a randomized code, some alpha-numeric code, and they would have a key that would link the research code back to the clinical code that is in the medical record. That key would be kept secured.

Then through this wall they would provide to the researchers on the other side the tissue sample with associated data gleaned from the medical record, whatever epidemiological data or factors that were requested, to the researcher. That's really where we left off, for the most part, last month.

Now, we made certain assumptions in proceeding further which you may or may not agree with, and which

we don't necessarily think are the only ones. But this is where we started trying to think about how we could maximize this type of paradigm.

The first, is that the samples in this situation contain under it a so-called blanket consent procedure in which the donor would agree to the use of excess of residual tissue for research and education, but it is unspecified because we don't know exactly what the research is going to be in the future.

CHAIRMAN MURRAY: Excuse me, Mark. Is this descriptive of how it's been in the past or is this your proposal for how it would be in the future?

DR. SOBEL: Well, to a great extent this is descriptive of what has been in the past, although actually in some situations I think there probably isn't even consent for that in some surgical consent documents, although I think in most cases there is.

But certainly prospectively, we can think of still informed consent where you know what research study you're going to do at the time you're obtaining the tissue even in a clinical context, but the vast majority of situations are going to be the ones we're

facing now where, four or five years later, there's a new potential use for the tissue that we haven't really quite thought through yet, so there's no, in my opinion, way to really have true informed consent for such future endeavors, except to call it whatever you want to use, blanket, general, unspecified.

So we're still saying you can get specific informed consent and do other things to the tissue. We're talking about situations in which this is the best we can do.

The second, is that the guardian would be a pathologist or clinical investigator with some special expertise with access to the medical record which includes the tissue samples and would provide a coded sample to research investigators.

Now, we are presuming certain things are in place. The first, is that confidentiality and security policies have been approved by an IRB in the setting of the guardian's department. That might be the pathology department or it might be an institutional-wide policy that has been approved.

Second, that because of the professional

expertise of the guardian, the guardian may be included, for example, as a co-author and get professional credit for this level of contribution to the work, but they're not otherwise involved so far in this scenario in the actual testing of the sample.

They are selecting the sample appropriately and that's their contribution to the study, which is, in fact, 90-95 percent of the time the contribution of the pathologist or the clinical specialist when they give samples out to other researchers.

Yes?

DR. HANNA: The implication is that the guardian has some clinical expertise.

DR. SOBEL: Enough to read the medical record and glean the appropriate information.

Now, third, that the research team would request the tissue sample and the clinical information from the guardian. The guardian would provide the research code, keep the key, then the research team would receive the coded tissue samples with the available clinical data that was extracted from the record.

Now, in this paradigm, as far as the research team is concerned, the coded samples are anonymous.

DR. EMANUEL: We don't use that linguistic phrase anymore.

DR. SOBEL: You can change that. You get the point, I think. Under this scenario, therefore, the research study could be exempt from IRB review. Now, the next point which I want to make, which is on my next flow sheet, is that no data from the research team can be linked back to the guardian of the medical record. That has to be a proviso if the research study is going to be exempt from IRB review.

So the next flow sheet is very similar to the previous one, and that's page 5 of your handout. But here, the data that comes from the research cannot get back through the wall. You're just not allowed to do it.

DR. EMANUEL: Cannot pass through the wall.

DR. SOBEL: Cannot pass through the wall.

Now, what are some possible scenarios? There might be additional requests. The idea here is to provide a mechanism within this paradigm by which

researchers could obtain updated clinical information and even additional sample, either more than the original number of samples, or they ran out of some sample and they need more to finish their study on the same clinical donor.

The point is, the mechanism should minimize the chance of research data, again, becoming available to the guardian and requests should be through some third party which, in this scenario, is a computerized, encrypted file. But it could be any one of a number of mechanisms.

So we drew this actually as a way around the wall, but still not in a way that the guardian could ever get the data. That could be through a stylized form because you don't want to have a scenario in which the researcher calls up the guardian and says, you know, Sample Number 14 is really interesting because it has A, B, and C, and then already now you have a break through the wall. So there would have to be some encryption. The guardian could look at requests and could then take this route to provide more information back to the researchers, but we'd never still see the

data.

Again, this is if you're going to have exemption from IRB review. If you're going to have IRB review in the proposal, then this going back through the wall could be part of your proposal and either you could get consent or you could ask the IRB for waiver of consent. We're not talking about those situations. We're only talking about situations in which we can liberalize the use of anonymous in the definition of --

DR. EMANUEL: I think actually that's not a good -- I'm going to object here because I don't think the rationale should be, how can we do it without IRB approval. That's not a good --

DR. SOBEL: No.

DR. EMANUEL: The rationale here is, how can you maintain the use of the tissue in an anonymous manner. That happens to track with because of 45 CFR 46 with not IRB approval, but it seems to me the rationale has to be, can we keep this stuff --

DR. SOBEL: Exactly.

DR. EMANUEL: -- sufficiently separated so that the two sides of the brain aren't talking to each

other.

DR. SOBEL: Exactly. Exactly. The point is not avoid the rule.

DR. EMANUEL: Right.

DR. SOBEL: The point is, set up a situation in which there is reasonable protection so that one can facilitate the research without having to go through many approval steps.

DR. EMANUEL: Right.

DR. SOBEL: The point being to facilitate the research, not to get around the rule. The end result would be --

DR. EMANUEL: I don't want to take up any more of your time, but, I mean, actually, as you present it it makes me more worried about this guardian rather than less worried. It was my main objection to the Merz article, was this idea of the trustee, because you've still got a person there who's got the file and has the link between the two and the consciousness of the two. If you could have that link separate so that that person actually doesn't know the code at the other end, that makes me feel much better.

DR. GREIDER: Which is Bernie's article.

DR. EMANUEL: Right. Right. Well, exactly. And part of what I had presented last week of having an encryption system where the guardian actually doesn't know the other end, which is the way -- I mean, on the Internet you have two --

DR. SOBEL: You can incorporate that within this scheme as well because the key could be encrypted.

DR. EMANUEL: Right.

DR. SOBEL: And all they have to do is access the encryption to say, researcher X wants more samples from 1 to 10, and updated clinical information for what we sent, and they push the button and then the key is mysteriously --

DR. EMANUEL: Right.

DR. SOBEL: I think that is within the context of this.

DR. GREIDER: The guardian is two people. Essentially, there's two separate guardians, whether they're physically together or one's a computer and one's a person.

DR. SOBEL: Exactly. Right. Okay.

But, again, this is all still within a scenario in which the guardian is not intrinsically involved in the research except in terms of the selection of the sample.

DR. EMANUEL: Correct.

DR. SOBEL: So far it's actually relatively easy. Now things start getting worse.

CHAIRMAN MURRAY: I'll just make a point while Mark is putting up his next one. In a way, if we want the actual results in terms of the ability to link the individual who is the source of the sample to the research information, the research outcome, to have a minimum of transparency you want to protect people as much as possible.

But I am concerned, as we get into these fairly elaborate schemes, how to protect data, that it goes against what we want. We want a system that we can explain to the public and to researchers as transparently as possible. Just bear that in mind.

We don't want to be able to say, you're protected because of a four-way computer network algorithm, we want to be able to say, look, there are

procedures in place that are reliable, trustworthy, and we can explain it in a relatively simple manner. That's a goal I have. Whether it's achievable, I don't know.

DR. COX: In a word, I understand why you're doing it because it's operationally easy, but to me it flies against the face of where everything's going as having walls between researchers and the people that are delivering medical care. To me, that's a non-starter because if anything is going to happen, it is that the people who are doing the research are getting closer to the people, not further from the people that are delivering medical care.

So, I mean, I'm very willing to consider this because I think it's a really helpful starting place in terms of a concrete proposal, but that's one aspect of it that really is troubling to me. Also, from the public hearings, people are saying, don't put a wall to me if there's useful information.

DR. SOBEL: Well, I heard that this morning as well as you did. But we started from a different starting point. I also want to point out, this could

also be used for samples that have been sitting around for 5, 10, 15 years, but still have some identifier on them and they could still be used now.

It might be quite impracticable to use the OPRR nomenclature in terms of getting waivers of consent for research to actually get consent from those patients, so the idea here is to open up some doors to make more tissue available and still protect people's privacy.

DR. COX: You're not saying it's easy --

DR. SOBEL: It's not limited to that, it's just one possible way of maximizing the use of tissue.

CHAIRMAN MURRAY: Can I just, procedurally here. A highly-placed source has informed me that we have until 11:40, because the other subcommittee is running a bit behind. So we have about 12 minutes.

DR. COX: Can I just respond to David. It seems to me that we have to be careful in using this metaphor of researchers and clinicians getting closer. They are getting closer, but we still may want to put up some barriers in the transmission of some kinds of information for reasons of other consideration. It

seems to me that --

DR. EMANUEL: We might. We might.

DR. COX: Well, I think if we're going to have tissue use in an anonymous manner, that, by definition, creates a barrier if it's going to be anonymous. I mean, it has to, otherwise the word anonymous is just a lie.

DR. EMANUEL: But I didn't think we were using that word anymore.

DR. COX: I think I used the correct circumlocution, which is that we were going to do the research in an anonymous manner, actually.

CHAIRMAN MURRAY: Sorry, Mark.

DR. SOBEL: So if we now think about how we could maximize the system, if you want it at all, you could actually think about having a research data repository which is, in a sense, anonymous and in which you could have the opportunity to store and retrieve research data on samples and records that carry the same research code.

This would be possible if the guardian provides the same research code to a clinical sample

given to multiple researchers at different times. Or you could link different research codes to the same clinical sample by having multiple keys and figuring those out. That would look like this.

So you could have cross-talk between researchers using anonymous samples without the guardian knowing what those are, so they're still anonymous and you still can't get back up here.

In this case, the guardian sends the sample to Researcher Number 1 and guardian sends either an overlapping or an identical set of samples to a second or more researcher. They can share information through some research data bank without every knowing what the clinical code is. So this is a way of maximizing information and use of anonymized samples.

DR. EMANUEL: Let me get this right. I'm at Hopkins, I set up a data base with all of my colon cancer samples, I put them into the computer, they're all encrypted, and anyone who wants to do research, say, logs on and can do the research and can find out what other people are doing with Sample 762. No one has any idea that 762 is linked to me.

DR. SOBEL: Yes.

DR. EMANUEL: Okay.

DR. SOBEL: Okay. So this would make more samples available to more people, and it would also mean that people would not have to do all things because they could benefit from what's already been done on the tissue. Or they could take a subset of that tissue once they knew what you had done at Hopkins. Okay. Then we're going to take the 30 that were this and work on it and be more focused.

DR. EMANUEL: Right.

DR. SOBEL: So there are many potential research advantages to having some sort of cross-talk here, but still not get back to the other side of the wall.

DR. EMANUEL: So that I carry the BRCA-I gene that is in this research data base, but not in the clinical data base, which we have no idea where that sample is.

DR. SOBEL: Exactly.

DR. EMANUEL: Okay.

DR. SOBEL: Now, the most problematic point is

the last one that I'd like to bring up, which is one that we really don't have great solutions for. That is, if the guardian is actually the researcher. So the guardian is not just selecting a sample and providing it to other researchers, but is intricately enough involved in the research that they are actually doing the analysis.

In the case of the pathologist, that could even be morphologic analysis or it could also be that the pathologist also does some genetic studies, or some transmissible studies, or any research study in which there might be some stigmatization or risk.

So here you're dealing with the fact that we started with certain assumptions again. Our assumption was that the guardian who's going to perform the research would still select the tissue samples and collect the original data from the medical record. You may find that you don't want to deal with that, but that was our assumption number one.

If that's the case, then point number two is that an IRB should be approving a policy for the selection of an appropriate second guardian, second

trustee--we called it steward--who could provide the research code and keep the key so that now the samples get anonymized and the guardian is, for all intents and purposes, the researcher on the other side of the wall, and I'll show you the flow sheet in a second.

Now, in order for that to be the case then we would want an IRB a departmental policy for confidentiality and security and we would also have the proviso that the data from the guardian's research team cannot be linked back to the medical record and that only the steward or the second guardian or trustee could provide updates on those samples.

So this really comes down to a matter of trust and faith. I can tell you that, at least in the pathology community, since many of these so-called guardian/researchers are pathologists, a lot of pathologists will be very offended by the very need to have the steward because they feel that they have signed the Hippocratic Oath, it is in their normal manner of professional behavior to keep confidentiality and privacy and, therefore, many people in the community will feel that this third party now that

we've put in this diagram is not necessary because they are following standard medical ethics of confidentiality and privacy.

But if you think of the potential risks of getting information back to the medical record and how soft that line can be, in this scenario we have included a second guardian who keeps the code and the guardian or other researchers can still cross-talk with the research data bank, as we showed before, but any more requests would have to go to the steward and would short-circuit the guardian so that the guardian should not be able to link research data to the clinical information.

Whether this is acceptable at all without going through the traditional mechanisms that we now have in place to consider this identifiable anyway because of the view of the tissue and the expertise of the guardian to begin with is an issue that you'll have to think about. If you want to consider this option, this is one scenario to accomplish it.

DR. MIIKE: I was just going to say, why not just deal with this as, we're linked anyway, right?

Rather than setting up this elaborate system when it's not -- I mean, if I were the guardian and I'm doing research, depending on the clinical information -- I can always tell. I can always go back in my data base and find out who that is.

DR. SOBEL: Well, again, this would be a situation of, in most cases, you still have the scenario that is the current regulations, which is that you would get consent or you would apply to an IRB for a waiver of consent because of the impracticability of getting such consent on extant tissues.

MR. HOLTZMAN: In what you're constructed here, does the guardian, and I'll move to this side of the world, do they or do they not possess knowledge that allows them to identify the subject?

DR. SOBEL: Well, I think that depends on -- in this scenario they shouldn't have enough information to be able to do that. So if you think that looking at the tissue block and having the surgical pathology number next to it and, at a later time, gleaning the clinical record and putting that together is going to, later when they do their biochemical test at the lab

bench, that they're going to remember that that tissue block that looked like that with that clinical information, that that's that case, then this scenario doesn't work and you can't identify it now.

MR. HOLTZMAN: You see, I think this formally collapses with all of these distinctions. That wall either does or does not define what's decided on based on whether you can identify.

DR. SOBEL: That's correct.

MR. HOLTZMAN: Okay.

DR. SOBEL: If the guardian can still identify the sample on this side of the wall --

MR. HOLTZMAN: Then it stays on that side of the wall.

(Laughter)

DR. SOBEL: See, we're talking about situations where that's not necessarily the case. For example, DNA is extracted from these samples and there are numbered tubes. The guardian is doing the DNA test, but they don't have the slide with them and they can't link it because they don't have the key.

DR. PITLICK: Mark, give the example of trying

to do antibodies on a slide.

DR. SOBEL: I mean, 90 percent of work that's done, at least in our department, is someone wants to check a potential new antibody for proteinase that has nothing to do with genetics at all, and they simply pull 25 cases of breast cancer or prostate cancer and then they move over to this side of the wall and they apply the antibody.

MR. HOLTZMAN: Mark, all I'm saying is that the salient point is not your title, where you live, the salient point is your histomological status. That's all.

DR. SOBEL: Right. So if you have extracted DNA from these samples and they are on this side and they have an alpha-numeric code, you can identify that sample and I think you can be on that side of the wall. If you are working with the actual block of tissue directly with the number next to it and that number is still there, then you can't be on that side of the block.

DR. COX: Mark, I'd like to make this point, hopefully not at your expense, but to use a concrete

example of what I mean about the whole picture. All right. When do people do research in the first place, if not to get it back to the medical record ultimately?

DR. EMANUEL: For the money.

DR. COX: Yeah, for the money. That's right. That's what it is.

(Laughter)

DR. COX: So if we come up with a structure that has the -- it completely fixes the problem of confidentiality but it doesn't address the issue of how research information gets back to people's medical records.

DR. SOBEL: But I would agree with what you just said. People do research to get back to the -- it depends on the kind of research you're doing. If you're not doing specific tests for the direct clinical care of the patient, you don't want it going back to the medical record. You do the research to increase your understanding of the biological process and you publish that and it's out in the public domain. I would say that 9 out of 10 times you don't want it there. There's no need for it to be there.

DR. COX: But that is not an effective way of getting information back to the medical record. It has not proven to be effective and, in fact, at the Task Force on Genetic Testing the main focus was on how you can have information of utility getting back into the medical record because there's no process in this country for doing it.

So, to me, this is a critical issue with respect to the tissue samples and it's not sufficient. I mean, this is something I'm --

DR. SOBEL: Maybe we're confused about the terms that we're using, because to me the medical record -- if you're talking about me, that's my hospital chart.

DR. COX: Yes.

DR. SOBEL: Okay. Now, if you do a certified test for, let's say, BRCA-I on my blood because I'm a suspected family and I gave you consent, then I do or do not want that in my medical record, but that's prospective, I've given my consent.

DR. COX: Yes.

DR. SOBEL: If we're just talking right now

that most of the recommendations of that BRCA-I testing should be on a research protocol and not go back to the medical record for a variety of very obvious potential harms that people are not protected from in our current society, then you don't want that back in the medical record and you either do the study the way the Human Genome Projected adjusted the Jewish Ashkenazi family study in this area, which was anonymous collection with clear understanding of the participants that they were not going to individually benefit from it, or you anonymize the tissue through one of the previous paradigms that I've showed you and the information goes out into the public domain for the appropriate groups to determine when it is clinically useful.

DR. EMANUEL: David, let's take the clinical samples, not the research samples. One of the problems of the research done here in an anonymous manner is people were collected in a cohort for --

DR. SOBEL: Yes, that's right. Okay.

DR. EMANUEL: So let's go to my favorite example, the angiogenesis factor and Judith Holkman's paper. So they go to the Brigham and they collect out

108 samples from 5 to 10 years prior to when they're doing the study. So here's the question: do you want to have a situation where they can then put that information into the clinical record or go back and contact the lady?

DR. COX: No, no, no, no. Okay. Let's use the situation of the BRCA-I. Just going out on our -- I'm just trying to be an advocate for some of these people that we heard. They're saying, listen, I want my stuff linked, because if you find something useful for me I want it to get back to the medical record. So they decide. We find out that there actually is a genetic test for which it predicts medical options. So we need to get back to those people.

CHAIRMAN MURRAY: We have a problem, in that we have to go to the joint meeting. We can come back to this.

DR. SOBEL: I mean, I think that's the other argument that we just discussed earlier this morning, is some people question whether it's ever ethically sound to anonymize a sample and use it in an anonymous way, and we have to decide what that's -- then within

this -- you have to decide --

CHAIRMAN MURRAY: Thank you.

DR. PITLICK: I just wanted to make an alternate comment. That is, what is the definition of research? Part of what we're trying to cope with is the afternoon crowds sitting around in the lab and saying, okay, now what should we do next, and doing something quickly that is not an NIH grant application, but is some quick study to look at, how does X relate to Y.

That's research as well, and that's the kind of research that is very problematic of educating people that they're doing research, that you need some kind of recognition of that fact. So there's research and there's research, and I think we need to deal with both situations. If it's very preliminary testing, you don't want that to go back in the --

MR. HOLTZMAN: I'm not talking about that.

DR. PITLICK: So you have to figure out, what defines research --

MR. HOLTZMAN: I'm not talking about that.

DR. SOBEL: I realize that. But we're trying

to work out a scenario. We recognize that that's going on, so you have to deal with it.

CHAIRMAN MURRAY: Okay. I think there's a will on the commission that you return after the joint session.

DR. SOBEL: Fair enough.

CHAIRMAN MURRAY: Thank you.

DR. SOBEL: Thank you.

(Whereupon, at 11:45 a.m. the meeting was recessed to go into Joint Session of the Genetics Subcommittee and Human Subjects Committee.)

AFTER RECESS

(1:40 p.m.)

DISCUSSION OF RECOMMENDATIONS/POLICIES ON THE TISSUE SAMPLES ISSUE

CHAIRMAN MURRAY: We're reconvening now the meeting of the Genetics Subcommittee. We still have with us Mark Sobel and Fran Pitlick to help us think through some of the issues, practical issues, involving the use of pathological samples.

Mark and Fran, I want to propose something to you before we get back into the conversation. That is, that you've given us an answer to a question that is a very important question for us. It presupposes an answer to a prior question, the one I think that David

Cox has been raising.

What if scientific information uncovered might, in fact, have clinical relevance and be the sort of information that we think it appropriate, and that patients would think it appropriate, to be fed back to them.

The analysis we've gotten from you presupposes the answer to that question is, there isn't such information. That will be many cases, but it won't be all cases. What do you say to that?

DR. SOBEL: I think that there very well might be situations. In the best situation, you would anticipate the potential use of some research information that might wind up going back. But, in that situation, you wouldn't use the paradigm that we're talking about here.

At least in our assumptions, using this we said that this would be used under a blanket consent, general consent, whichever way that worked. But I would say that, if you had a situation where you anticipated this information and would back to the clinician and/or the individual donor, that that can't

be used in that scenario, you would have to use an informed consent procedure with specific IRB approval for your policy.

And if you thought it would be particularly impracticable because you were working with archive samples and you wanted to invoke the impracticability waiver issue, then you would have to make a proposal to the IRB and convince them that you could waive informed consent.

So you would have a set of prescribed policies and scenarios. If such and such happens, this is how we'll handle such potentially relevant clinical information. We'll send it back to the IRB for decision, we'll go back to the primary physician. There should be a well laid out framework for dealing with such scenarios.

So what we proposed here was not those situations, but only situations where you do not anticipate.

CHAIRMAN MURRAY: So did I characterize correctly that you have, in fact--given the answer to the first question--the answer is, no, we don't think

it will be this kind of clinical information, generally. Then here's what you're proposing.

DR. SOBEL: There are a couple of examples that this commission has talked about in situations where research has gotten into sticky situations and gotten into a moral dilemma because they basically were using the samples as if they knew that somebody could break the code and they found something that they thought might be clinically relevant, such as HIV status or something, and they came up with this moral question, now what do I do, what is my obligation to the individual? But I didn't get consent. That's been handled in various ways. I'm not so sure ever very well.

So I think the more we anticipate these sorts of problems, the recommendation should be that there should be, just when you write your grant, if protocol A doesn't work, I have two other ways of answering my question.

I think that people should be anticipating these questions. If there is a legitimate chance of that happening, it can't go through this or it has to

go through a specific protocol, IRB approval, informed consent.

DR. PITLICK: I would like to add, I talked with Roger Almott who was here earlier, who is the project officer for the Cooperative Human Tissue Network. I said, how great is the pressure to go back, to get information back to the physician? And he couldn't recall a case.

It turns out I knew of a case which was a tested HIV status, and when I mentioned it he recalled that, but essentially there's a mechanism at NCI that's been working this way and they've had one incident that they recall when there was a perceived urgent need to go back.

They finally decided, well, that wasn't a CLEA-accepted test. They were not doing HIV studies, they were doing HIV to protect their assays, to protect their own laboratory workers. But it wasn't a clinical assay. So they've only had one instance in the Cooperative Human Tissue Network. It would be fairly rare if we started out with this situation.

DR. COX: So the person wasn't told because it

wasn't a cleared test?

DR. PITLICK: That's right. And the decision was, it turns out the person was -- there was a lot of discussion about it and the decision was at the Cooperative Human Tissue Network that the information will not go back, period, for anything.

DR. SOBEL: Now, in this scenario that we've proposed, because we have the wall, somebody does have the code. So there should be a possibility. I would give you an example of a misdiagnosis, for example, that the guardian sends out 50 cases to the researchers of supposed dysplasia of a particular tissue, and the researchers realize as they're doing it that one of the cases is, in fact, not dysplasia, but a frank cancer and it's medical malpractice, number one, and number two, there's a patient out there with cancer who doesn't know it who could potentially be treated.

How do you deal with a situation like that? Well, there, I think, you could go to the IRB, for example, in my scenario, at least the way I thought it through, and say, I have this potential medical situation where there's a potential therapy for a

disease that has been missed and we want a procedure approved to get contact back.

Now, how exactly that could be done, I would leave up to the IRB, which might be too much of a burden, but at least they would be an impartial third party. So I could see certain scenarios like that.

Another scenario could be, I decide that I'm not going to let my laboratory use tissue unless we do test for HIV and hepatitis no matter what and I send it to a CLEA certified laboratory and I get --

DR. MIIKE: Your first scenario, what you would try to change is if you're not sure whether you could get back to the patient on time or --

DR. SOBEL: Well, in my scenario you could get back because someone is holding the code.

DR. MIIKE: No, no. What I'm saying is that the patient might have already died, versus intervening on time.

DR. SOBEL: But I couldn't know that because, to me, the sample is anonymous. So I would have to say this is a misdiagnosis, and I would have to get that information back. But in order to avoid the guardian

learning too much extraneous information that you don't want to do, you really need a third party, which to me would be an IRB.

I think it would be a very rare situation. This should not be something that happens on any routine basis, but it might potentially happen and you might want to consider having some sort of loopholes in there that adequately protect privacy, but still can protect the person. If it then turns out that they break the code and the person has died, then that's another issue because you still have a potential medical/legal case.

DR. EMANUEL: I think it's very important for us to appreciate these cases. But, as I think we said last time, appreciate the fact that --

DR. SOBEL: These are exceptions.

DR. EMANUEL: Well, not so much exceptions, but everyone is going to have a different judgment as to whether it's a good thing to go back and trace and release the information or -- and we've been alerted of cases, and there have been cases in the literature, where people have done that and it's been a mistake.

Someone didn't want that piece of information. They thought it was important, and it turned out to be something someone doesn't want. I think this is going to be a serious, serious problem anytime we allow this exception.

For one thing, allowing the exception -- and I'm not arguing against it or not, but we should be aware, the moment that barrier really isn't a fire wall but sometimes you can overcome it under these conditions, the more we allow that as a possibility the more we increase the chance for problems both ways.

I mean, one of the great advantages of it really being a fire wall, you can't go back, we've thrown away the key, is the fact that it goes both ways. You don't have an abuse and you don't have a problem where someone gets a piece of information and they didn't want it.

DR. COX: Zeke, I completely agree with you. But what I'd like to do, it's not these rare exceptions. I quite agree, right now that's the way it is. But I'd like to just put forth a scenario that is not very crazy, I believe.

It's epidemiologic studies done in a big metropolitan area with the patients being from a conglomerate of different HMOs and those were the exact individuals that re being used for the research. And you're blinded, so you've got your fire wall up.

Now, Carol, you're right, it's published in a peer review journal, it shows clinical specificity and sensitivity with certain measures. HMOs are going to want to use that information in those very patients to save money. You're going to tell them they can't use that because the same patients -- you're not talking about one or two patients, you're talking about a big sample of individuals that are going to be able to change their medical care and the health care costs. That's the way things are going right now.

DR. EMANUEL: But I don't understand. They're not going to go back. They're going to have to either repeat the lab-derived test -- but that's true for every HMO in the country, David. I don't understand how it's specific.

DR. COX: It's specific because it's a different way of practicing medicine because the

patients are the subjects. So the research subjects are, in fact, the patients. The information, it's epidemiological studies, Zeke, that are being applied to the population that you're doing the study on.

DR. EMANUEL: Okay. So let's take an example. We're going to go to all the managed care organizations in Northern California and we're going to screen them for some colon cancer gene.

DR. COX: Exactly.

DR. EMANUEL: Okay. That, you know, whatever, triples your risk for colon cancer.

DR. COX: Exactly.

DR. EMANUEL: Okay. We've got the fire wall up. We've identified that you can do this cheaply and easily.

DR. COX: And you identified two percent of those people where you did your study. In fact, the study was done to show sensitivity and specificity. It was done on hundreds of thousands of people, right?

DR. EMANUEL: Right.

DR. COX: And now you're going to go back and you're going to redo those tests?

DR. EMANUEL: Yes. Right.

DR. COX: It's the same reason that CDC isn't going to go back and spend $2 million to do informed consent on the enhanced people, because you already know what that two percent of people is. Somebody knows it, but you have no way of getting that information back right now because there's a fire wall.

DR. GREIDER: I'm not sure what your concern is.

DR. COX: No. It's just a practical concern, Carol, of whether you're going to then -- so you found this information out. That's the way research is right now, right?

DR. GREIDER: Right. Uh-huh.

DR. COX: But what I'm saying is, when it's large numbers of patients -- we're not talking about small samples of single things, but costly experiments to go out and do the tests, you're saying we'll just pay for it again. So you know what the result is in the patients, you've done the studies, but you're not going to use the information and you go back and the HMO will just pay for it to find out. They'll just pay

for it again.

DR. GREIDER: Why would they pay for it again? Why would they even do it again?

DR. COX: No, because they don't have the results. They can't get the information. They've had their patients -- actually, they're part of the researchers, right, because they're the people that are donating, the patients.

DR. EMANUEL: They're the guardians.

DR. COX: They're the guardians. Right. So the information is obtained, you have proven your general scientific point, but the actual data is of medical utility to those specific people.

DR. GREIDER: But they wouldn't normally do that anyway. They wouldn't normally go out and screen 100,000 people for --

DR. COX: That's not the way medicine is done today, but that's exactly what's coming down the pike.

MR. HOLTZMAN: The whole notion of the world starts with the idea that we want to have information that's flowing in one direction because it benefits the study. We're anticipating here, to your language, a

case in which the goal was not medically relevant information, not medically relevant information -- whether it's for one or for 5,000.

So now the question is, are we going to permit in any case for it to flow back, and since we can't anticipate every case, if we're going to provide for that formal possibility then it's going to be via some kind of mechanism.

DR. COX: Exactly.

MR. HOLTZMAN: So in your case, David, I'm just taking that as the sum of many cases.

DR. COX: Precisely.

MR. HOLTZMAN: Where, if there's going to be a motivation that's going to be -- it's going to have to do with the medical benefit.

DR. COX: Absolutely.

MR. HOLTZMAN: Okay. You were pointing to a little different point, which is the economics.

DR. COX: But the benefit had to be there to begin with. That goes without saying.

MR. HOLTZMAN: To begin with, right.

DR. COX: Without the benefit, just research

information without clinical utility, and I use that point clinical utility being equivalent with medical benefit, something you can actually do with the information.

MR. HOLTZMAN: So as I'm thinking here about writing a report and a set of recommendations, Zeke has laid out one argument that says, as soon as you allow for that formal possibility, then you will have destroyed the necessary sense of integrity and trust that goes into it being truly a fire wall, the cost, effectively, would be too high--social cost--and so, therefore, better that those cases not get the medical benefit than we erode the crack in the wall.

DR. EMANUEL: No, no, no. It's not that they don't get the medical benefit, that you create a different procedure for getting the medical benefit, right? You publish the data, the HMOs then take on the data or practitioners take on the data and decide if this is a good test to use, and we use it in this kind of defined population. That's what we do all the time.

MR. HOLTZMAN: Right. But I think what we are anticipating here is time-sensitive information that

comes up.

DR. SOBEL: But in your scenario you're talking about a very, very large, hundreds of thousands of people being studied.

DR. COX: Or small, either one. I use that to both examples because you could take the arguments, well, this is so rare, it's never going to happen. The other situation, you could say, it's so costly that no one will ever do the test again.

DR. SOBEL: But most of the time, see, the medical community does not really generally accept one report, however large the study is. It usually takes a little bit of time to incubate, so you have quite a bit of a time delay by the time you do the research, write the paper, get it published.

Then, after the first report, when you have a potentially high suspicion that you're onto something, then you wouldn't do the study this way. Then you would do it with consent and with identifiers.

DR. COX: This is the way it's done. Are we going to do the NHANES twice? I don't think so.

DR. EMANUEL: No, but NHANES is a different

story. That's not the right story. I mean, the right story here is, we're an HMO and for some reason we bank samples on 50,000 of our patients, blood samples on them.

Now you want to say -- I mean, I can just tell you, having talked to these managed care executives, we're going to give it to researchers to run tests and we're then going to ask the managed care, go back to those people to tell them we've got a result on a test they didn't even know was being done on them? No way.

DR. COX: No, no. They're going to know it's done on them, Zeke.

MR. HOLTZMAN: The individuals won't know, is his point.

DR. COX: Yes, they will.

DR. EMANUEL: Well, wait a second. The fire wall.

DR. COX: Under the scenario we're laying out right now.

DR. EMANUEL: I think we need to go back to this framework. If it is a previously collected sample with no consent on it, not even general consent, or is

it a prospectively collected sample -- I mean, right not if you go into the Harvard Community Health Plan, or any health plan, they don't prospectively consent you to use your samples in a general manner. They don't.

Now, maybe they will after our recommendations, although I still doubt it to some degree. So let's distinguish those two. I mean, if it's prospectively done and people have had an opportunity for consent, I mean, one of the possibilities we could raise is, do you want to be informed again.

But I think we need to recognize, the moment we have that exception for informed again, we're going to have a lot of situations where people didn't anticipate that their stuff was going to be used in a manner or for a kind of test that they may come back to, especially the moment we get all the -- you know.

DR. COX: That's what this whole discussion is about, Zeke. That's exactly what this discussion is about. So do we or don't we basically have the patience involved in the kind of prospective studies?

I mean, I think this is right on the target of what we're discussing, but it's a different scenario case than --

DR. GREIDER: I think we're in a different box.

DR. COX: I am in a different box.

DR. GREIDER: I like having Zeke's boxes, because we're jumping all over the mountain with the boxes. We've got to take them one by one.

DR. EISEMAN: Can I give an example that might help? I think you're talking about a prospective study, is that correct, where we're going to start this study now, you have 100,000 people and try to come up with a test for this. One good example is something like the Women's Health Initiative.

DR. COX: Perfect.

DR. EISEMAN: They have women who are -- on one arm of the study it's a hormone replacement, and to be on that arm of the study, one of the tests that you have done up front is an endometrial biopsy, because they don't want to be giving women who have hyperplasia or malignancies any kind of hormones that might

exacerbate their condition.

DR. COX: Absolutely.

DR. EISEMAN: Within that consent, those women are informed that if some abnormality is found with their tissue, which goes through a CLEA-approved pathology department, they will be informed.

DR. COX: Exactly. But that's a very different scenario than what we were talking about.

DR. EISEMAN: But part of that consent also says, we're going to take some blood from you and that blood will be used for future research purposes. The information from that future research, you will not know. There are ways to --

DR. COX: Perfect. So I'm a happy camper because there's two different things.

DR. EISEMAN: -- informed consent.

DR. COX: But the way that it was presented is that the first part of that that you showed was not even on the radar screen, that is, the part about going back. The only point I'm trying to make --

DR. EISEMAN: Because this is collected samples, a different block.

DR. SOBEL: We started off with all these samples in which you didn't have informed consent, and the presumption was that the only way to use it was to anonymize it.

DR. COX: Fine. So what we've done, is we're really only talking about part of the picture.

DR. SOBEL: That's right. Absolutely. That's the starting point.

DR. EMANUEL: I think, David, the whole picture, maybe, on this, but I believe Mark and Fran's discussion was related to the previously collected samples where we have not had a process of fully informed consent, and I think it's important for us to go over what we mean by fully informed consent because it may not turn out to be --

DR. COX: That wasn't at all clear to me. If that's what you meant, I didn't hear you say it.

DR. SOBEL: But it could also be that, after your report comes out and you have your recommendations and people put into place those recommendations, there are going to be all these situations where you do collect samples and tell people, I'm going to use some

of your residual tissue in the future for some unknown reason. It's this blanket, unspecified --

DR. EMANUEL: General consent.

DR. SOBEL: -- general consent.

CHAIRMAN MURRAY: And they agree to that.

DR. SOBEL: And they agree to that and it's sitting in a bank somewhere. Then someone comes along with a research idea and wants to use it, but it's going to be difficult to get consent specifically for their study.

DR. COX: No, no. I'm not asking for that.

DR. SOBEL: So then we've broadened the term "anonymous" and used this fire wall approach where, if you have a prospective study and you know it, then there's no reason not to get informed consent up front.

MR. HOLTZMAN: But the go-back issue --

DR. COX: Yes, but the go-back issue, what about the go-back with prospective studies?

MR. HOLTZMAN: See, the go-back issue is going to resurge again. We can deal with it here, but -- let's deal with it here and then we'll deal with it again. Okay?

DR. EISEMAN: But it's like the way Sheri has it set up in her paper. As soon as a sample is in storage, it's no longer a prospective study. We're now talking about studies on already existing tissue.

MR. HOLTZMAN: Right. But we're projecting a different framework. We may come up with the same solution for the future uncontemplated study and the serendipitous result with medical implications for both.

DR. EMANUEL: I mean, let me just say, the headings here are an attempt to reflect and reconstruct from the transcript the changes on every single heading we made. It's not retrospective, previously collected, where previously refers to the date we would expect full implementation of the recommendations of this report, and we had collapsed here clinical care and samples collected for research into all, that they should be treated all the same way.

Then we had, following Steve's recommendation, said that we should not refer to the tissue but to the tissue to be used in an anonymous manner, the way the research is conducted or tissue to be used, and I

should have put, an individually identifiable manner here. Okay. So these are essentially the current pathological or current specimens in pathology departments now where consent has not been obtained.

DR. COX: And I'm a happy camper on this piece. It's not a problem.

DR. EMANUEL: Now, the flip side is, samples to be collected in the future, that is, after we expect implementation on the basis of our report, and there are two types, those collected for clinical care or with no known specific research project or those with the specific research project in mind. Okay.

Now, I take it, David, and maybe here is where we've had the confusion, your suggestion or your problem has been that you thought we're not only talking about these kinds of studies --

DR. COX: I did, indeed.

DR. EMANUEL: I mean, for these studies, and I don't want to speak for everyone else, but I thought we had come to some conclusion that, in fact, we should be talking about a kind of general consent here if they're used in an anonymous manner. If they're used in some

identifiable manner, full informed consent.

I think it may be useful, as I was sitting here, for us to think through what we mean by general and what we mean by fully informed, in part because, on a preliminary gut reaction, the only thing that might be different between those two consent forms is, what are the objectives, how specific are you on the objectives? Because the risk may look very much the same, the benefits may look very much the same, and the alternatives may look very much the same, you just may not have a very specific idea about the --

DR. COX: That's the point I was making, because it gets to be a very slippery slope to know when you want to be general and when you want to be specific, because you can't predict ahead of time, at least I can't, when useful stuff is going to come out of the research and when it's not. Okay.

I can't tell you ahead of time when the great, unexpected thing comes by, it's basically going to be the magic cure for AIDS. But I don't want to be hindered based on what I told them ahead of time, if I find that cure, to be able to go back and have it

applied. That's the rub.

But you do have the advantage, in a prospective way, of talking to people about exactly this point. But I will tell you why I am being a pain about this, is not what I believe, but what I perceive the public believes, which is that it is not -- I mean, it's not the public and the people that we've heard speak aren't sort of very much looking to the well-being of society, but they're really looking to the general well-being of themselves.

I mean, they believe if they give this stuff, irrespective of what anybody says, that stuff will come back to them. I mean, that's what people believe.

You say, well, you know, this really isn't -- I've informed people jillions of times, just as have you. You say, you know, this really isn't going to mean much to you. And they go, yeah, we know, but we know that if you find something you'll let me know. So I really think this is a critical thing.

DR. EMANUEL: Take the BRCA-I research done here where they put together the Ashkenazi Jewish population. They were specifically told that they were

going to make it anonymous and they can't walk back. They will not get their own results.

DR. COX: Yes, I know that.

DR. EMANUEL: I take it that this falls into this category right here. We don't know who it is. Give us general consent, we'll talk to the community, we'll get some IRB approval, but we're not walking backwards and telling you, even though some percentage of those women obviously came out positive. We were able to do --

DR. COX: But the reason I don't have problems with that, Zeke, in some ways is because of the kind of utility part of it. I mean, that part is just missing. So this is all sort of theoretical.

CHAIRMAN MURRAY: There have been two people very patiently waiting to get in, then Bette. It's Fran, Kathi, then Bette.

DR. PITLICK: My point that I wanted to make several minutes ago, is to realize that you probably don't look at hundreds of thousands of samples until you've done some preliminary work.

Maybe the model that we're presenting is

particularly appropriate for initial studies or background information or whatever to develop what your more serious big sample is going to be, if it's going to require, or may eventually.

But you probably wouldn't even go into a big, full-blown study like using this model without a little study first that was going to tell you what you wanted to do and how you wanted to do it.

DR. HANNA: Yes. I just wanted to briefly make the point that I think in the report we're going to have to be careful to make a distinction between research and clinical, because in the example you're using presumably if you know something has clinical utility, you're not going to embark on a 100,000 person screening project to determine what the gene frequency is, or whatever.

In the BRCA-I example, it wasn't until they got good information on who were more likely to be carriers of that gene and what the clinical relevance might be that it then entered the world of clinical utility and then women that could participate in the study could go and be tested versus being screened.

DR. COX: They still have good information, Kathi.

DR. HANNA: Well, no. Forget about whether it tells them they're going to get breast cancer or not. I mean, that's a big issue. But it then becomes a matter of choice for those individuals, whether they want to be tested and find out what their individual status is.

I just think that at some point the research protocol either falls into clinical utility or not, and then the rules -- it goes into medical practice and, as far as I'm concerned, out of the research realm, where the individual is concerned.

DR. COX: This is the box that it's in right now. I understand what you're all saying to me. I understand how unhappy anybody is of thinking about it this other way. All I'm asking is just to think about it for a second, that there isn't this sharp line between clinical medicine and research. That's all I'm saying.

The kinds of experiments that are going to be happening are going to be ones that blur that line even

more. It's not because we're intentionally just making our lives more miserable, but it will blur it because of the kinds of studies that are done. If you can do a small pilot study, this is not an issue.

Many of these things, in order to get the results, cannot be done as small pilot studies, they're going to be done as big pilot studies, and they're not going to be done twice. It's a new way of doing science, a different way than we've done in the past. So maybe that's not what this commission needs to worry about, but I just --

DR. EMANUEL: The question is, don't we have a box for it, and in what way does the sort of suggestions --

DR. COX: And you've been very helpful, because the box is definitely over on this side, which is, in fact, definitely in the prospective, so that's crystal clear. I think, retrospective, we're trucking along. We're in good shape. If this prospective --

DR. GREIDER: So we haven't -- groups yet. I mean, right? Retrospective with the groups still gets back into the same area.

DR. COX: No, no, no. I didn't say we're done, right, I said we're shaping up.

CHAIRMAN MURRAY: I think we're shaping up. We're not in good shape yet. We have a winter's worth of hard exercise ahead of us.

DR. COX: But this is a very -- it's outside of tissue samples. It's the issue of a different line between medicine and research. We're going to face it. We're going to face it head on in the human subjects regulations.

DR. HANNA: But I just think the research clinical distinction is important for the person who is giving consent because it tells them something about what promises are being made to them, even though in reality it is getting blurred in the laboratory and in patient care.

DR. COX: Yes. But can I just say, and I want to really simplify this and then I won't say it anymore, this is -- so I'm talking to the person, saying, listen, we're going to do this research. We don't know anything about this right now.

Something of clinical utility may come out of

this or not, clinical utility meaning a piece of information that I would use to make a medical decision with respect to you. All right.

But if that kind of medical information comes out, then it's an obligation, I'll get back to you and we'll use it. Right now, I practice medicine and we don't do that. We don't do it because it's too hard.

People, with a wink and a nod, they say I'll do my best, but that's not a contract, because we don't have a mechanism in this country set up to deliver medicine that way. Well, are we going to? That, to me, is a really important question. If we aren't, then I agree. Then let's not say we're going to do it. But if we are, then let's have our ethics with a mechanism for doing it. That's what is of interest to me.

DR. EMANUEL: Yes. But that's beyond our control, David, I think. I mean, that's beyond the purview. What we're here to do is to set up rules, I think, about how you can collect them, what kind of promises you can make, and if you make them, what are you supposed to do?

I think it's helpful here because I haven't

found, now that we've looked at those boxes, a disagreement. I think, actually, we're in agreement. If you're doing this as part of research and you might anticipate going back to those people with your results, that's in the informed consent.

DR. COX: You just said something that's very interesting to me. You know how pragmatic I am, but I don't think we're here to set rules. I think we're here to think about what the big picture bioethical issues are, and then have suggested ways that we can pay attention to those. But the rules, to me, aren't the primary thing.

DR. EMANUEL: Well, I think a lot of the communities are looking to us to establish for them, under what circumstances can they use the previously collected samples, under what circumstances do they have to go forward. It's inevitable whether we're going to make the rules, whatever you call that.

DR. EMANUEL: Clinic was the same. But just to go back to clinic, what we did, was we had bigger issues.

DR. COX: That's right. We don't need any

legislation. I mean, we may not need legislation, we may need interpretation.

MR. HOLTZMAN: Even with the prospective ones.

DR. COX: Right.

MR. HOLTZMAN: Where, in step one, you're going to specify, this is the study I'm going to undertake, and you can specifically say with respect to the output of that study, if it has clinical relevance, you either will or will not be informed and you gain your consent on that basis. If you have a further provision with respect to that sample, that it will be used for further unspecified research.

Then you're going to have to have the question, with respect to that further unspecified research, do you or do you not want to be informed and contacted, under what kinds of conditions? Either you're going to have that kind of provision or you're not. I think we need to have a set of recommendations with respect to that.

DR. EMANUEL: I second that.

MS. KRAMER: I'd like to come back to that. I was one of the people who, at the last meeting, was

feeling very strongly that there was a responsibility to create a way in which we could go back, that that responsibility flowed from the use of the tissue.

I'm really changing my mind, because it's beginning to feel too much like you're trying to make public policy or public policy recommendations based on really an infrequent exception, which I think you really can't do.

So if, in fact, it really takes many studies before it comes to a conclusion, then that is almost in the process going to identify a group that is vulnerable, and then that is going to be highly publicized, whether it's the breast cancer mutation, colon, or whatever. A person is likely to know that they're a part of that group. But I think now it comes back to just what you're talking about in either the extant tissues or the prospective tissues.

If they've lent their tissues, if they've consented prospectively, if they've consented for their tissues to be used in a particular study, they're going to know, depending on the publicized results, where they fall in that study. But I think that if they want

to let their tissues be used for further future unspecified research, that maybe that's where they --

MR. HOLTZMAN: That's where you're going to have to deal with it.

MS. KRAMER: Right. But the thing is, should we give them the option of saying, yes, I want to be, or no, I don't want to be notified, or should they be required to be notified?

DR. EMANUEL: Well, let me give you an example that I thought about because of a friend of mine. His mother has early Alzheimer's. So the question comes up, his sample might be used for perfecting another Alzheimer's test with no better therapy than we have now. Would he want to be informed?

MS. KRAMER: No. He already knows he's a part of that group.

DR. EMANUEL: All he knows is he's at risk. He doesn't know what his risk is.

MS. KRAMER: That's right. That's true. But he knows he's at risk, that's what I'm saying. So he will know, as the results are publicized. He will know. If he doesn't want to know, until there is such

a time when something can be done about it, then that's his option.

If the time comes when something can be done about it, he already knows he's a part of that group at risk and, therefore, believe me, that will be well publicized. You won't have to be sophisticated to have that in your face. So he will have the option of going and finding out.

What I'm concerned about is, suppose now they take the tissue from the people who have been used to establish early Alzheimer's and they say, okay, we're going to take this and test for something else and, in fact, they come up with a positive result. He might not know that.

There is no reason why he would be expected to know that, particularly if it turns out that it's just a small percentage. I mean, if the whole group was, I guess then again he would know. So that's where I'm concerned.

MR. HOLTZMAN: There's a range of cases and examples, and it's useful to think through them all if we're going to come to something general. So if you

focus on a serendipitous finding of a predisposition to a late-onset fatal disease with no possible intervention, if that's your paradigm, you're going to conclude that there's no good done in going back to the individual. Okay?

MS. KRAMER: Clear.

MR. HOLTZMAN: If you think of something like a serendipitous finding of HIV, or maybe not HIV but something which is readily preventable --

DR. COX: A curable cancer.

MR. HOLTZMAN: A curable cancer. You're going to be inclined to go back, particularly if what you found is definitively known. I'm using a marker. I'm using an S&P and a known gene. Okay.

Then you're going to get the sort of gray one where it's, well, do I really know something? For example, working with people in Zeke's institute, we have discovered a gene which it looks like when it's down-regulated indicates invasiveness of melanoma, and early intervention is critical.

We've looked at a bunch of samples from Zeke's institute, unlabeled, et cetera, et cetera. The

pathologist could tie it and someone who they're calling as probably non-invasive based on the phenomenological measures, we see that gene off. Okay. We've only looked at 45 cases so far. It's 45 out of 45, up until this case. So it's a research result.

Should that physician do anything about it? A common sense reaction if I was in that reaction? I'd probably want to call that patient back in, not to say you have something, but I'd probably want to go look again. Okay. So let's not focus in on any one of those cases, but recognize the range of cases. I think then when you consider that range you end up coming back to Zeke's proposition.

Is the inviolability of that wall back, the precondition of having a wall that people can be good about, or is the potential for cases in which individuals can benefit, the weight of that, sufficiently great that we should provide a mechanism by which it can be breached, and if so, what is the structure of that mechanism?

DR. GREIDER: And not only that, we can't base that decision on the way things are currently done and

the frequency with which it currently comes up. Taking what David said, you have to anticipate, will the frequency of these kinds of things increase in the future, are we likely to stay the same. I think I agree with you, that they are more likely to increase than not.

MR. HOLTZMAN: Well, if you take genetics, when you move from anonymous triplet repeats as your marker, you're moving to common variants and the S&Ps representing common variants, you know what's going --

MS. KRAMER: So is it too much of a simplification to say, okay, is the potential for violation of impermeability greater than the need or the anticipated or possible future need to go back. So we're not going to be able to have both.

DR. GREIDER: If you set it up appropriately I think that you can.

MS. KRAMER: Okay.

DR. GREIDER: Because we were talking about double-blind kinds of studies where you can go back and still protect individuals.

MS. KRAMER: How can we take this and start

doing it then?

MR. HOLTZMAN: I'm not sure -- explain what you mean. The double blind says -- but Zeke's point is, you've reached back, even though for all of the protections where the people on this side can't go back, you're allowing a possibility to allow the people who can go back to go back. It's in the nature of the case, if you can come one way you always can go the other way. So the question on the table is whether we're going to allow those who can, to.

DR. GREIDER: But you don't make it a simple thing so it's not a fortuitous, accidental going back.

MR. HOLTZMAN: No, absolutely. Right.

DR. GREIDER: But if, under the circumstances of IRB approval of going back --

MR. HOLTZMAN: Now you're articulating a mechanism.

DR. GREIDER: Right. With the appropriate mechanism, that there is the appropriate coding so you can do it, but it's not going to happen in an accidental way. One problem of setting things up so that there's a wall and it only ever goes in one

direction is very easy to protect. But if you want to have things sometimes go back, then you want to be really sure that the mechanism on the other side is very robust. So then you want to argue for an extremely robust protection mechanism, if you're going to allow it, to go back under some circumstances, of review and approval, et cetera.

MR. HOLTZMAN: So now if you would assume that robustness of the confidentiality in your procedure, the next thing you have to focus on is who will make the decision to allow one to go back and what will be the relevant criteria or parameters that will be in play?

DR. GREIDER: The same IRB that sets up the path on a protocol.

DR. COX: But I'll tell you, the Genetics Testing Task Force went through this, and I think that was not anything I'd like to use as an example of how to do things, but the real bottom line that came out of that was, how do you determine -- because the key factor should be the clinical utility, how you determine clinical utility when it's scientifically

valid and has clinical utility.

Mechanisms for doing that in this country -- I mean, it's very, very difficult in -- to know. In fact, how stuff gets used right now and how that gets determined is not very pretty.

DR. GREIDER: That's why I go to the IRB.

DR. EMANUEL: But we should be clear.

DR. GREIDER: That's why you should go through some sort of a --

DR. EMANUEL: But if you keep going through the IRB, then we're piggy-backing or being parasitic on a process which, first, was not set up to do this at all, and second of all, we are beginning to tax a system that has absolutely no funding and it's going to collapse under more and more demands.

MS. ALPERT: An instructive scenario that is currently going on. The Mayo Clinic apparently, from what I understand, has a mechanism to do exactly what you're talking about. They have a separate body within the clinic to look at clinically relevant findings, incidental findings, from genetic research and they go through that board to see whether or not they should

inform the patients or the research subjects.

DR. COX: Exactly. And whether they have utility. So I must say, maybe you would view this as a cop-out, but I don't have any problem in saying that the measure has to be clinical utility and there has to be some mechanism which we're not setting up right here to say there's clinical utility.

But, once there is, then our mechanisms are going back and kick in. But it's what Steve is saying, to me at least, that we have a process for going back. Zeke, I would like nothing better than to have that wall not breached. It just doesn't pass the sniff test to me in terms of where people are out there.

DR. HANNA: When you talk about clinical utility, do you mean specific to the disease for which that individual first came in, or anything? So they came in for breast cancer, but you found out about Alzheimer's.

MS. KRAMER: And there's clinical utility in what you found out about it.

DR. HANNA: Right.

MS. KRAMER: Something can be done about it.

DR. HANNA: The only reason I'm raising that, is that can be, I think for some individuals, a much more troubling scenario. I just know this from when I worked in clinical genetics. They came in for advance maternal aging and you checked their family history, and you find out there were all kinds of other things they should be more worried about and it was very upsetting to people.

DR. COX: I agree, Kathi. But what I'll also tell you is the way you take care of that is the same way you deal with non-paternity, which is you bring it up when you first see these people --

DR. HANNA: As a possibility.

DR. COX: -- about the possibility. Then some people are going to feel very strongly, some people aren't. I don't think you can have a lot of different lists, but it's what you tell people up front. I do have problems -- I don't know.

I have much more problems with these things that are found with additional studies that were done on their samples that they didn't know about. I mean, that is getting into a very gray area. It's not such a

gray area, though, of studies that they're set up on to get this stuff back to them.

DR. EMANUEL: Yes. But, David, that is, I thought, the scenario we're really worried about. We've taken your sample for X. You have participated in the Physician's Health Study, or whatever, and we've taken your samples for X, but suddenly, five years later, we've discovered a new test we want to do. Say someone comes up with what they think is a very good predictive test for Alzheimer's and they want to do it.

DR. COX: Yes. But I'll tell you, Zeke, the reason why in the past I wouldn't have had trouble with that is if work was being done on an anonymous fashion and you didn't have any easy way of getting back to people. But if we have people all linked up, then we do have a way of getting back to them.

So then I have much more of a problem because there's a code and a way to get back. Then, to me, the obligation shifts. The expense doesn't get any -- maybe it gets a little bit less, but the ethical obligation shifts, for me.

DR. GREIDER: To where?

DR. COX: To informing the people. This is only in the case, though, where you're in a situation where you have something you can do that's really going to be life-saving to those people. The interesting thing is, the American Society of Human Genetics is shifting in this same way with respect to going back and telling relatives.

What happens if the individual doesn't want to tell their relatives, and you can do something that basically you know will save that relative's life, do you go back and tell them? There was a big discussion at the annual meeting and they're shifting over to say, yes, in those situations where you can really do it, it's okay to tell them and, in fact, you should tell them. That's what they do in the rest of the world.

Boy, let me tell you, people just went ballistic, the counselors and the medical geneticists about that, because they had this different ethical view of looking at things. So we're on very shifting sands here in terms of what the obligation is of going back or not going back.

CHAIRMAN MURRAY: Fran?

DR. PITLICK: Are we still talking about that upper left-most corner box?

DR. COX: No, no. We're done with the upper left one.

DR. PITLICK: Well, I can't figure out what your scenario is about whether we are --

DR. COX: The scenario is prospective studies.

DR. PITLICK: Okay. So it has required -- okay.

DR. COX: No. Listen, from the upper left-most box, going back to those people and all those things that are stored --

DR. PITLICK: But in some of these cases there wouldn't be a fire wall, and that is, in a sense, what's confusing me. If there's a fire wall, you're dealing with an anonymized situation.

MR. HOLTZMAN: We are dealing with the upper left-hand box as well. You have to recognize that.

DR. SOBEL: The samples are going to become that, except for the fact that they gave blanket consent.

MR. HOLTZMAN: Right. I mean, effectively,

right, what we're talking about is the uncontemplated study.

DR. COX: Yes. But the difference is, Steve, you weren't able to talk to them ahead of time.

MR. HOLTZMAN: Right.

DR. COX: And I make a big distinction between those.

MR. HOLTZMAN: Yes. But it's effectively not that different. All right. If it's in the box today and the person --

DR. COX: Ethically it's not, but practically it is.

MR. HOLTZMAN: But the argument is that practically, with respect to the sample I collect tomorrow, the consent I will get for the study that I can't envisage yet is that I'm going to do studies which I can't envisage. To me, that's tantamount to the general consensus we got yesterday.

DR. COX: No. But you will have talked to the people and told them about that, whereas previously, okay, you didn't. That's a big difference to me.

DR. MIIKE: What if when you talked to them in

the beginning you said, I don't want you to tell my relatives. You just told me that they are moving toward telling the relatives anyway.

DR. COX: In some situations, that's exactly right.

CHAIRMAN MURRAY: That's in specific clinical interactions. Yes. I want to put the family aside for next year.

DR. COX: It sounds to me like you're not going to come up with a rule, but rather come up with a list of exceptions.

DR. EMANUEL: Wait a second. There is some benefit here in speaking to the boxes. I don't know whether it's these or other boxes, in part, because we're mixing and matching and there may be a consistent set of exceptions or a very definable set of exceptions which Steve has outlined that is going to run throughout the boxes, where you have general consent, recognizing some future test, and it could be in some of these either studies or clinical situations 5 or 10 years down the line where you end up getting the test that may be relevant to them because there's now a

therapy available where there wasn't, so it was useful to examine these things.

But it seems to me one of the differences is, if we're agreed that there's going to be some kind of general consent we also have to recognize that probably the general consents you're going to get in a research setting is going to be different than the general consent in a clinical setting because, you know, if we're talking about a research setting there is probably going to be a moment where there's a researcher in the room and the patient or subject in the room.

If we're talking about the clinical scenario, there very well may never be that moment, in part, because what we talked about is that when there is a clinician and a patient in the room it's the wrong time to ask these questions and we're talking about maybe going back afterwards or going before.

DR. COX: That's absolutely true.

DR. EMANUEL: So I think keeping those separate is also going to keep in our minds different kinds of paradigms for how this is going to work. The

other thing we might want to remember is that part of what we talked about last time, and again, I don't think we've come to a conclusion, is a general consent for research studies but an opt out for a clinical situation.

Not a consent, an opt-out scenario. A presumed consent with an opt out, because, precisely, we wouldn't have this interaction, which I think may mean that in the clinical situation the barrier for going back has got to be a lot higher.

MR. HOLTZMAN: I completely agree. We need to work through your trunk. And not only the specific boxes, but if you think about the Weir paper, which I do think kind of laid out some of the conceptual framework that people are using, or we've rejected something which you have in your upper left, or we've said effectively that the clinical versus research collection distinction with respect to its existing samples is unimportant. In our paper we need to say why we believe that.

CHAIRMAN MURRAY: Or we need to give justifications, reasons for all of these judgments.

DR. COX: But no one is placing any big distinction on the fact that -- I see. But you're making the point--I'm slowly getting this--that there actually is a clinical versus research distinction because if there's a researcher in the room the researcher can then tell people about it, but if the clinician is in there and would be just collecting it, you can't tell them. But it's not worth making that distinction in terms of just lumping them together.

DR. EMANUEL: Well, if you look at the previously collected samples, then my paradigm is, samples that are now stored in Stanford University versus the Physician's Health Study -- in the Physician's Health Study they got some kind of consent, but they didn't anticipate all of these genetic tests when they originally collected them.

They certainly didn't anticipate immortalizing the cells. Similarly, when they collected the clinical sample there may be a line of that in the consent for the surgery, but no one read it, and certainly no one, as best as we can tell, observed it.

So I think it was some of those considerations

that led us to believe, well, really, in some sense these are materially the same kind of samples. People didn't consent, either generally or specifically, for this.

DR. COX: Either way.

DR. EMANUEL: Right. On the other hand, in the future, if you think about the clinical scenario, well, there's not much we're just going to change in the clinical scenario that's going to give you a chance to get an informed consent, either a general or a full informed consent, because at the moment where someone is consenting to get their colon lopped out or the breast biopsied, they're in no mood to hear about research, storage of the sample, et cetera, and they won't remember it. It's just not going to happen. So there, if we sort of think of an opt-out system, we're going to send them a form and if they object they can send it back, it's likely to happen in a situation where there's not going to be a clinician there talking to them.

Conversely, in the research setting, if you are going to get something like a general consent for

use in an anonymous research study, then someone will be in the room, the opportunity for explanation. On the other hand, if you want an identifiable sample, then they have to give what we call full informed consent for this specific research project.

I do think at some point we should talk about what we mean in our minds, the difference between full informed consent and general consent, because, again, I submit there are differences, but they're not maybe as great as many people think.

DR. COX: Because, Zeke, you're making the distinction between people going in and getting their big toe cut off and somebody uses it as opposed to people that are enrolled in research studies. When I think about clinical stuff -- I didn't get this out of the transcript. I mean, I see it now, of lumping the stuff that comes out of the -- extra material from clinical stuff that the pathologists have. That's actually what you're talking about, too.

DR. EMANUEL: Right.

DR. COX: Right? In your whole scenario, all of this was over in the left-hand box. But that's very

different from people being involved in clinical research studies.

DR. EMANUEL: Right.

DR. HANNA: If it's just a population study, we don't have a medical record. Presumably you don't have a medical record assigned to it.

DR. GREIDER: But even if there isn't a medical record --

DR. COX: Right. Not a medical record. You might have a research record.

DR. HANNA: Right. But you don't have a medical record so it's different.

DR. COX: I must say that I have much less trouble with that than I do with the research studies because right now in the research studies we don't go back to people. We don't do it. We say we do it; we don't do it.

CHAIRMAN MURRAY: Which research studies, David?

DR. COX: The clinical research studies.

DR. EMANUEL: NHANES. Take that. The NHANES-III. They're not going back.

DR. COX: They're not going back. Exactly. But do the people know that?

DR. GREIDER: Well, they know they're in the study.

DR. COX: Yes. But do they know that no one is going back to them?

DR. EMANUEL: I think in NHANES they do, actually.

DR. COX: I would really question that.

DR. SOBEL: This reminds me of when the Heart, Lung and Blood Institute had a panel to discuss the Congressional demand that all these blood bank samples should be used for AIDS research and they went back and looked at what kind of consent they had obtained to obtain the samples and, in fact, they found that half the groups couldn't even find their informed consent documents at all, and those that did, it depended on how it was written.

Some of them said specifically HIV, some of them said viral so that it was possible to do hepatitis. But if they didn't say infectious disease and they said viral, then they couldn't go back and do

parasite studies, which are now important.

So that's the paradigm for, you can't predict, way back, the potential uses for information. The other part of that discussion was that some of the blood bank directors said that within one year they lose track of 50 percent of their donors.

Now, we had a discussion this morning that it's possible, on the Internet, to eventually find someone's address. But I don't know how the staff time is involved in doing that, especially in medical centers where you have people coming from different areas of the country for expert care and you have a very mobile population in this country anyway. You're not going to have very good trackability anyway, except in the longitudinal studies where that's the real purpose.

DR. COX: Yes. But in that exact situation of the Heart, Lung and Blood that you talk about where the patients were collected under specific informed consent for a specific thing, then if they weren't given the opt out for the types of research, then what do you do? Do this prospectively, now.

So what should you do in the future, and should you allow them to opt out or should you just say that your stuff is going to be used for other research studies too? I mean, this is what we're talking about here. It's in a research setting. That's where most of these samples --

MR. HOLTZMAN: Well, they don't come up mostly in research studies. I think what you're going to find here is that what is most problematic is the pragmatics of --

DR. COX: That's where the samples are now. Right.

MR. HOLTZMAN: -- that the clinical collection, all right, because all of the things that you might ideally want in some ideal world built into robust consent. It's just not going to be possible to build it into the clinical situation.

DR. COX: Okay. But let me just say to me -- and I agree with that, Steve.

MR. HOLTZMAN: Okay.

DR. COX: It's certainly true in terms of what the numbers are, too. But then let's make this really

strict distinction between prospective clinical research where you're talking to the patients and when you're not, because I think that that's very different.

MR. HOLTZMAN: Again, we really need to work this through. That's why we felt it was important to keep that distinction --

DR. COX: Alive.

MR. HOLTZMAN: -- with respect to the things we're going to collect tomorrow. Now, where you're going to run into the graying is when, even in the research setting, going forward when you start to think about the studies you haven't thought of yet and what is the nature and content of the consent in that instance.

DR. COX: Well, so I'm very happy to have my mind opened to this, but I think it's too key, by half, to basically take the samples that are collected in a research study where it's prospective in talking to patients and saying, okay, now they're already collected and they fall into this other category.

DR. EMANUEL: No, no.

MR. HOLTZMAN: We agree with you. We agree

with you.

DR. EMANUEL: I think up at the top where it says, "Samples collected in the future," the meaning there is samples collected after we publish our report and we think that regulations ought to have been implemented and that people have had time to think about the kinds of consents.

My own challenge to my fellow commissioners is, try to think about the kind of general consent form, either in the clinical setting or in the research setting, where you want it to be general that you would have. Here's my attempt, and it's not very satisfactory. I'm just not happy with it.

I think it's a problem and we need to try ourselves to think about the kinds of things we think ought to fall in there and the kinds of things which we think might not fall in there. Think of all the examples that we've just brought up, because one of the things that I don't have in my thing here is, do you want to be contacted back.

MS. ALPERT: I had put a little bit in my paper about it. The OPRR and FDA have come out with

their revised lists of what's eligible for expedited review. This is a notice for comment out in the *Federal Register*. One of the things that they -- and this may or may not make a difference but I just wanted to highlight it, this was not in the old list.

"Research involving solely A) prospectively collected identifiable, residual, or discarded specimens; or B) prospectively collected identifiable data, documents, or records where A or B have been generated for non-research purposes."

So what they are saying now is that they are including clinical data or clinical specimens for expedited review.

CHAIRMAN MURRAY: Including identifiables.

MS. ALPERT: Absolutely. That's all that it is. So I just thought I would --

CHAIRMAN MURRAY: That just means --

MS. ALPERT: It -- the review, but it's not --

CHAIRMAN MURRAY: As opposed to full review, exempt from the review, or expedited. This is expedited.

MS. ALPERT: Right. It's a truncated approval process.

CHAIRMAN MURRAY: It's administrative review.

MS. KRAMER: Zeke, can you and others circulate these? I understand that they're just working papers.

DR. EMANUEL: They're so embarrassing, but I would be happy to.

MS. KRAMER: Well, to me, I don't even know where to start.

DR. EMANUEL: Well, I'd be happy to Xerox it and send it around.

MS. KRAMER: Yes.

DR. EMANUEL: This was an attempt at the opt out for the clinical anonymous in the future. This was an attempt to define an opt out using the National Coalition's thing. It just was not -- I spent a couple of hours on it, but it's not so easy. That's all I have to say.

DR. MIIKE: Well, I mean, but there's a diminishing utility since most people are not going to pay attention to it anyway. They're under duress.

DR. EMANUEL: No, no, no. The question is, if you send this to them, say, a week or two after they're in the hospital or a week or two before they're going to come in the hospital so they're not under that kind of stress. You're going to send this to them and if they don't want it -- you'll see the structure of it is, if you want to check off any of these boxes you send it back in the enclosed envelope.

CHAIRMAN MURRAY: If we don't hear from you --

DR. EMANUEL: Right. If we don't hear from you, we presume that you're going to participate.

DR. MIIKE: There are problems with that.

DR. EMANUEL: Well, as we heard from BRCA --

DR. MIIKE: Is that a default opt out or a positive opt out, because you're describing a default opt out.

DR. GREIDER: Presumed consent with an opt out. If you don't send it back, you're in the study.

DR. EMANUEL: Well, you're not in the study. Your sample could be used for some future study.

DR. GREIDER: Right.

DR. EMANUEL: But it says here quite clearly,

one of the things I put in there, that it's highly unlikely. Importantly, the vast majority of tissue samples are never used for research which, from what we gather, has to be true if we have more than 100 million samples.

DR. GREIDER: But that won't necessarily be true in the future.

MS. KRAMER: But that's disingenuous. Right. Exactly.

DR. COX: See, this is actually what I'm worried about. We have the 100 million samples. This is the point, actually, you brought up, which is really a good one. It's not the number of samples, but it's what gets popular to be used, because if researchers use a set -- that's why there's all this business about the different institutes.

There's this group of samples that are taken and people glom under those. They say, I want to do my stuff with that group, and then more and more people use it and it gets used for more and more things. That's exactly what I'd rather not see happen, because that's the better chance that people are going to be

unhappy campers.

DR. MIIKE: I'm just thinking of the logistics of this. You get discharged from the hospital. Who sends it, the hospital or the doctor?

DR. EMANUEL: The hospital.

DR. MIIKE: Then so how many thousands of letters are we going to now be responsible for in a year? Would I include it with the bill? No, I'm going to do a separate mailing.

DR. EMANUEL: No, I agree with you.

DR. MIIKE: I see all kinds of operational difficulties.

DR. EMANUEL: But, Larry, here's the question. If we're going to give people an option to opt out and it's going to be meaningful, or you could do it the other way -- I will just tell you, if you want to do it as an opt in, only people who say yes, the answer is --

DR. MIIKE: I think the simplest way to opt in or out is, here's your consent form. Instead of burying it in paragraph 78, after you sign the consent form there's a little thing, P.S., your tissue may be used in research in the future for some unspecified

reason; do you also consent to this? Just highlight it away from the general form.

DR. EMANUEL: And P.P.S., I forgot I even read that and signed my name to it. That's what we're hearing. I can tell you, that's what the studies show.

DR. PITLICK: But I don't think that the consent forms usually had a specific line about research in --

DR. EMANUEL: Usually the line they have is that, we're a research institution, we use these samples for research and education, just to let you know.

DR. COX: And, Zeke, there's an additional part to this which I think that we, as a commission, have a big impact on. It's not just what you write down, but it's what people say. A person has to hand you that piece of paper, at least that's the way it happens right now for surgery and things.

No matter how upset you might be, if anybody ever asked me if I cared if my stuff was used for research or not, then I might forget because I was upset, but I'll guarantee you, I'll have a much better

chance of remembering if they had never even mentioned it and it was on the piece of paper. So it's what you say in addition to what the paper says, too. It's how you inform people.

If you have, as you said, that thing written down and then a person says, yes, there's a second part to this which basically doesn't have to do with your operation or anything but it has to do with any tissue that will be left over, do you agree to research or not.

MR. HOLTZMAN: Yes. But what we've heard about with respect to that moment when a person is coming in for a biopsy, they think and they're afraid they have cancer -- all right. We heard two things. First off, it's not clear that you should be talking to them about the research use of their tissues in that context, just as a human matter.

DR. COX: It's not that that's --

MR. HOLTZMAN: Right? Number one. And then number two, if you do, that the likely interpretation of that is one of being coerced because, were you to say I don't want my sample used for research, that you

may not get as good care because you have offended the doctor. So, I mean, the take-home I took from that, from opposite ends of the spectrum, is that is not the moment to be trying to get full-blooded consent.

DR. COX: No, I agree. So what other moment do we do it?

MR. HOLTZMAN: Well, that --

DR. COX: Because there's two choices. We either find a better moment, which I can absolutely agree with, or we take that moment that presently exists and we do it better than we're doing it now.

MR. HOLTZMAN: Right. And my conclusion is that --

DR. SOBEL: Which also means educating hospital personnel, the clerk at the entrance room who is usually the one that does it, who is not particularly educated about it.

DR. EMANUEL: We have experience with that and it doesn't work particularly well. We should all be aware of that.

DR. COX: So another moment, that would be great.

DR. PITLICK: How about at discharge? Is there any experience with hospital discharge, doing it then?

DR. EMANUEL: Well, you know, with outpatient mastectomies, what discharge is there anyway, anymore? I mean, the discharge is when you're half under anesthesia.

(Laughter)

MS. KRAMER: My experience has been that there is a certain amount of papers and forms that you have got to fill out and sign off on prior to entering the hospital not even necessarily the day you enter, but a day or two days, or whatever, before.

DR. GREIDER: So you know two days ahead of time.

MS. KRAMER: Right.

DR. GREIDER: Assuming you know two days ahead of time. The times that I've gone into the hospital I didn't know two days ahead of time.

MS. KRAMER: Well, okay. Right. Exactly. So in an emergency case it's going to be different. But, insofar as -- I don't know what the majority of cases

are, but I would imagine that the majority of cases are non-emergency cases.

So if it could be attached to those papers that need to be taken care of on a preliminary basis, yes, sure, you're anxious about it, but at least if you're confronted with it and need to sign -- maybe what needs to be done is, maybe there does need to be a separate, additional signature for a statement that says either I consent or I opt out.

DR. MIIKE: I'm getting more to the point where I'm saying, we don't really need to pick a specific set of recommendations because this way we're -- I mean, we have the unscientific focus group discussions on which we cannot rely in a valid fashion.

DR. EMANUEL: Because we don't have IRB approval.

DR. MIIKE: Not only that, but because of whatever.

What if we come to the conclusion that we are swayed that informed consent, et cetera, et cetera, are so important that they're worth all of the operational research impediments.

If we are swayed that research really is what -- there's nobody really objecting to research -- do you know what I mean? I'm trying to set up sort of an alternate scenario that if we get swayed one way overly versus another way, that then we come up with easier ways of recommending some of these things.

So that in terms of the informed consent side, if we're swayed that research is a good thing, we still need to worry about informed consent, maybe we can protect it on the back end by the kinds of things that, once you get into the actual research design, the whole issues about confidentiality.

I don't know how you deal with individual instances or very unique sets of circumstances or the exceptions to the rule kind of a thing, but it seems to me we don't have to come up as a body and say, this is the way we've got to go. We can give them a set of choices. Whatever we come up with is not going to the ones -- nobody is going to accept the recommendations -- right? They're looking for wisdom from us.

DR. COX: They will if they agree with what they already thought ahead of time.

DR. EMANUEL: But here's the issue, Larry. I think you're right, but the question is whether we're going to require some kind of consent or whether something like presumed consent with an opt out would be acceptable.

Do you see what I'm saying? Because one possibility, you know, might be that you have to say yes. In a clinical setting, afterwards, I could use your tissue only if you said it's okay to use your tissue.

Another option would be, and I think Martha was the one who started us rolling on this is, we're going to use your tissue unless you have objected to it. We've given you a reasonable opportunity to object to it.

So I think those are the kinds of different things that we have to struggle with or come to some conclusion on, because they lead to different kinds of -- you know, not necessarily different kinds of procedures, but, at least conceptually, potentially different kinds of procedures.

DR. COX: I think the opt out, personally, is

a very good compromise. It's definitely a compromise. But just in terms of logistics, it gives the person -- it empowers the person to do something. The person has to be awake. He can't be asleep at the switch.

DR. MIIKE: But if you don't opt out, then what?

DR. COX: We are going to use it.

DR. MIIKE: What is the informed consent if you don't opt out? What's the consequences of opting out, are we still going to --

DR. SOBEL: This will not affect their clinical care.

DR. MIIKE: What I'm saying is, are the safeguards any different if you opt out or you opt in.

MS. KRAMER: Safeguards for?

DR. GREIDER: Your tissue is not used if you opt out.

MS. KRAMER: Right. Exactly.

DR. GREIDER: End of story. It's not in the research.

MS. KRAMER: That's it. Yes.

DR. EMANUEL: Then we could use your tissue if

it became relevant to a research project.

DR. MIIKE: So even if we put in an opt out, you still have to deal with -- are obligated to do for --

DR. GREIDER: Absolutely. I thought you were saying that's presumed consent.

DR. MIIKE: I know. But then just the whole issue about --

DR. EMANUEL: I'm not sure what you mean.

CHAIRMAN MURRAY: If someone agrees to opt out, if someone says, I don't want you to use my tissue, that's the end of the story, right?

DR. GREIDER: Well, what about the other people?

DR. MIIKE: Your opt out or opt in choice is overlaid on this. If you opt out, you're out. If you opt in then it's used. This is what you propose?

DR. GREIDER: Right.

MR. HOLTZMAN: This is with respect to specifically the concept of opt out and how it came up in clinically collected with respect to use in an anonymized fashion.

DR. GREIDER: The upper left that's showing right now. In the future, clinical care, anonymous.

MR. HOLTZMAN: Right. No one has suggested so far that opt out would be an appropriate mechanism for future identifiable research, particularly if collected in a research context. We might come to that.

DR. GREIDER: It's just in the -- column.

MR. HOLTZMAN: Right. So let's take it as -- Zeke's suggestion is with respect to clinically collected samples that one could use an opt out as the mechanism of consent for future studies conducted in an anonymized fashion.

DR. EMANUEL: You understand? So we take out your colon tomorrow.

MR. HOLTZMAN: Or the day after. It's up to you.

DR. EMANUEL: And in the future we want to run a test, we want to enter your colon into a research study. DR. MIIKE: We're not having an opt-out provision in the research setting?

DR. EMANUEL: No. The research setting, you do that in --

DR. GREIDER: 1A that is showing.

DR. MIIKE: In a research study, I don't understand how it would --

MS. KRAMER: There isn't one.

CHAIRMAN MURRAY: You're asking, would you participate in the study.

MS. KRAMER: Yes, there is. There is one. See, in the --

DR. EMANUEL: That's for community.

DR. MIIKE: I don't have any problems with an opt out because opt outs, I know most people won't opt out anyway so there's going to be very little difference in what happens. So it's going to make us feel good, but there's not going to really be much of a difference.

DR. EMANUEL: No. But here's the question.

MS. KRAMER: But you're covered. You've done the decent thing. You've given them the opportunity. If they don't choose to take it, okay.

DR. EMANUEL: Maybe the conclusion we want to say is, we're putting too much emphasis on the consent part of this story and the opt out is, we're doing

something but not full-blooded consent because we think full-blooded consent is, first of all, where you can't find a good time to -- if we found a good time it would be enormously expensive, plus it wouldn't be full-blooded consent because we still --

DR. MIIKE: That's why I think that once you are doing the actual research itself, absent the kinds of things that David would want to add in, I think that's the more important part.

DR. EMANUEL: Fine. That's the boxes on the right under Research Studies.

DR. MIIKE: Yes.

DR. GREIDER: The fire walls, you're talking about.

CHAIRMAN MURRAY: After you then take the tissues and actually do whatever you are going to do to make them research tissue.

DR. MIIKE: But especially on the clinical side, I mean, I don't see the content or the substance of consenting to something you have no idea about what's going to happen down the road. It's not consent.

DR. EMANUEL: But, Larry, just take something like the Physician's Health Study or the NHANES. You can't consent to a very specific study, right? Some tests might come up in five years after you've --

DR. MIIKE: But at least you know you're consenting to be a research subject. That's really different from the clinical side.

DR. COX: You can consent though to the fact that your stuff is either going to be used in a research or not. Now, some people would say, that's no consent because you don't know. Well, it means something to me. I know what research is. Somebody is going to take it and they're going to do stuff with it.

CHAIRMAN MURRAY: Look, it's worth reminding ourselves what consent was about in the first place. The idea was to prevent the abuse of human beings in research, to prevent them from direct physical manipulations and harms.

That's the condition of the kind of core or paradigm case for why we regard consent as a sacred thing on human subject research. That's it. We are several steps removed from that kind of model in this.

We also think that in those situations you ought to tell people exactly what you're going to do and exactly what the risks are. This is, again, several steps removed from what we're contemplating here where we might not do research for 5, 10, 20 years later, asking questions and using methods and tests that weren't even invented or contemplated when we originally gathered the sample.

So I am feeling the need for a little reality testing on my own part to sort of get us back to what's important here.

DR. EMANUEL: But we did hear from Bob Weir. I mean, there's a heavy emphasis in his approach upon the importance of consent, as it were.

DR. MIIKE: I'm going to get back in because David is.

CHAIRMAN MURRAY: We've taken it as a -- I think bioethicists have tended to treat consent as a kind of all-purpose solution.

DR. EMANUEL: I agree.

CHAIRMAN MURRAY: Zeke, I know you agree. We should not see it either as an all-purpose solution or

an all-purpose want for doing everything we want to do. So it's okay for us to be thinking creatively about some alternatives to the usual models.

MR. HOLTZMAN: I think something we need to think about here, because again, as we take positions they need to be articulated against the positions that have been taken. So jumping ahead, I believe where we may come out with respect to future unspecified uses of samples collected in a research context, and we're going to have some sort of general consent. So then if you believe general consent is more robust, okay, then --

CHAIRMAN MURRAY: Presumed.

MR. HOLTZMAN: Presumed consent. Okay. Then the argument has been made on the one hand that that's okay because, in some sense, the person getting clinical care owed a duty back for the clinical care they got, and on the flip side, the argument has been made, no, no, they're more vulnerable than the person who is in the research context, that at least the research subject consented to the research enterprise to begin with. So what is the justification for a

difference in the level of consent between those two cases? All right.

Is it in principle where we're adopting one of those arguments or, in fact, are we simply resting it on the pragmatic ground, so to speak, that in the clinical context the general consent, if collected at the time, effectively is empty so you might as well go to a presumed consent, whereas when you have the research subject there you can, in fact, get a valid general consent, if general consents are valid at all. I think we have to walk through these things very systematically.

DR. COX: But the people --

CHAIRMAN MURRAY: Does that make sense, by the way?

DR. COX: Yes.

MR. HOLTZMAN: I think that's right. I think that's the challenge.

DR. COX: But the people in a non-specific study, in terms of voting with their feet, said that they would rather not have a presumed consent, they would rather have a general consent.

CHAIRMAN MURRAY: I don't think you could infer that. What I heard them say is, we'd like to be asked. All right. Opt out is a form of being asked.

DR. COX: But opt out is a general consent, as far as I'm concerned.

CHAIRMAN MURRAY: You could do an opt out general or specific. I mean, that's the difference. It's a question of what are you saying, am I opting out to all possible uses of research, am I opting out of the specific --

DR. COX: When you say presumed consent --

MR. HOLTZMAN: Okay. So let's get our nomenclature clear.

DR. COX: -- what does presumed consent mean? That means presuming --

DR. EMANUEL: Let's stop. Let's walk back from full-blooded consent. Actually, I think this might be helpful if we -- do we have a blackboard?

CHAIRMAN MURRAY: Go ahead and use the flip chart, Zeke.

DR. EMANUEL: Okay. These are the three categories that we've been dealing with. Now, as I

understand full informed consent, here you outlined the specific objectives, the benefits, risks, and the alternatives.

Here you have a very specific research project in mind. We're going to test it for ABOE, we're going to test it for BARCA-I. Here you have only general objectives, general benefits, risks, alternatives. We should be clear that the alternatives is basically no research, right? No go. Okay.

Now, here all you can say about your objectives is, you're interested in research. And you may not even know the area because you might collect it for a cancer study but end up using it in some diabetes work. Therefore, the benefits are very -- there's no specific benefit for you, is basically what you have to end up saying.

DR. COX: What some people will say is, you collect it for a cancer study, use it for a cancer study.

MR. HOLTZMAN: Well, in between you could make class distinctions.

DR. EMANUEL: Yes. The usual thing we've

heard in this situation is, any research, the disease for which the sample was collected.

CHAIRMAN MURRAY: But you've already pointed out the problems with that.

DR. EMANUEL: Right. Then this, no genetic, following the National Coalition, whatever. Any research was one possibility, specifically for cancer, specifically for anything but genetics. I tried to implement some of that in what you're going to get, and I guess Henrietta is going to fax it tomorrow. That's very hard to do.

Risks we don't know, and the alternatives are, you know, just pull your sample. But at least with this you have an idea that it's going to be used for research. Now, presumed consent is, we're going to use it unless you say no, and we give you an option of saying no, either a checklist option or just a no. Now, the checklist option might be disease-specific --

MR. HOLTZMAN: Same categories as --

DR. EMANUEL: -- or genetics. Right. These have been the two that have been cited in the past, but, again, we're free to make suggestions as we go.

So I don't know if that's helpful.

DR. COX: It is helpful.

DR. EMANUEL: Here, what presumed consent means is I'm going ahead unless you tell me no.

CHAIRMAN MURRAY: In the clinical samples, maybe 1 in 100,000 might actually be used.

DR. EMANUEL: Right.

CHAIRMAN MURRAY: But then I have the permission to go ahead at this point.

DR. COX: But, see, there's a presumed opt out. We're in a situation right now where we have presumed, no opt out.

DR. GREIDER: No, no, no. It's presumed in, but you can opt out.

DR. COX: No, no. I understand. But what I'm talking about is the situation that we have right now, which is researchers say, I'm pretty sure that everybody actually wouldn't really want me to use their stuff --

CHAIRMAN MURRAY: We have this, informed consent that may mean nothing.

DR. COX: Yes. That's why I was confused.

CHAIRMAN MURRAY: It's not presumed consent, David. People sign. Much of it is, particularly in recent years.

DR. MIIKE: Can I ask a little tangential question. Suppose we get a system to say disease only or for everything. How are you going to follow this on the samples? How are you going to get that marked down with the samples that, oh, you can only do research for cancer, this one for --

DR. EMANUEL: Two things on that. First, there is a medical record then that captures the sample and you can have a slot in the medical record. We have slots for lots of things in the medical record now, the original consent to undergo the surgery, advance directive stuff. I mean, it's not difficult, it seems, to put an entry in there.

Second of all, if you really believe that the electronic record--I don't know when it's going to come, but it's coming--there you just have a field and if you can't use it for research, it pops up red.

DR. EISEMAN: That's how they do it in the Women's Health Initiative. If people opt out of

genetic research, it's entered in the data base with their code for the person.

DR. MIIKE: But that's a research study, isn't it?

DR. EISEMAN: Right. But then they've opted out. And none of those samples --

DR. MIIKE: I'm just thinking in terms of your usual medical record.

MR. HOLTZMAN: The thing about the pathology samples and what's asked, couldn't one have in the pathology samples something which says, not to be used for the following kind of research?

DR. PITLICK: We assume so. All of this adds other -- everything we're talking about adds administrative --

MR. HOLTZMAN: Well, it's one more field. It's not clear to me that that marginal cost of one more field in a relational data base is that much.

DR. COX: Yes. But, see, whether anybody pays attention to it -- okay. So it will be in there, but whether people actually pay attention to doing that.

DR. EMANUEL: I think we need much more

discussion.

MR. HOLTZMAN: I think a very important thing for us to consider again is, insofar as these distinctions are made, we hear people using genetic testing versus other. If one of the things we're coming to is that that's not a very useful distinction, we might wind up recommending that that shouldn't be what's being used here.

CHAIRMAN MURRAY: Right. And one thing I contemplate as a possibility in the recommendations we make is that some of the conclusions that we are led to might, in fact, be conclusions that have a kind of open-ended empirical -- like, we've made some observations about the current function of these little forms that people check off in a clinical setting for the use of their tissue.

I feel pretty confident about those observations. Maybe our recommendations will be for opt out or our recommendations will be for a more full sort of consent at the time even though it's not optimal. One of our recommendations is that we need to study to see what, in fact, the impact of this is.

So we might call for empirical studies to, in fact, affirm or disaffirm what we think might be happening, and then to change policies accordingly. I don't see that we have to sort of say something once and for all -- we can say, look, we recognize that we've made assumptions in our own recommendations.

DR. COX: I really agree with that. Doing things like we just did in terms of laying these things out so people get their nomenclature right, so we really see what the options are, then there's no way we're going to have the data to say what the impact of choosing one or another of these is.

This is what you were saying, Larry. I mean, it's more sort of laying out the process rather than the rules. It doesn't mean we won't have potential rules, but we don't necessarily say, this is the way it should be done.

MR. HOLTZMAN: I would submit to you that there is a very large part of the research community that is waiting for this group to come forward with a set of recommendations about how and under what conditions these things can be used. All right.

CHAIRMAN MURRAY: What I was saying wasn't that we shouldn't make any specific recommendations. I'm saying we could make recommendations recognizing the assumptions built in, that they may be incorrect, but we should also then suggest ways to sort of -- so that we can -- next year our recommendations are implemented, in five years are even going to be something better there, and we ought to lay out the architecture on those things.

DR. COX: If we could know how to do it, I'm happy to do it. But I go back to the cloning report, because there were significant bodies of people that had high expectations for specific recommendations for us in that scenario, too. I think if we can make specific recommendations based on the facts, I'm happy to do it, but if we can't, I'm not so keen on that.

DR. EMANUEL: Here's a suggestion. Under samples to be collected in the future, clinical care, to be used in an anonymous manner. There we might say the following. We think the minimal level of consent should be presumed consent with an opt out. Some institutions may want to go to a general consent.

Now, we don't know exactly the best method. It hasn't been tested what the best method for presumed consent with an opt out is. It might be on the surgical consent form in an extra paragraph. It might be that you ought to send out a form two weeks later. It might be that you want to send a form when they come in for the pretesting, if it's an elective surgery. All of those would be reasonable approaches.

We estimate, you adopt any of them now, we hope that the field studies them to find out what the most efficacious is, but these would be acceptable, you know, that kind of thing. That seems to me to be a reasonable regulation with built in the idea that you can experiment in your local community, but you can't just presume everyone is going to consent.

DR. PITLICK: I think one of the most significant recommendations you could make, from my perspective, would be the ability to use tissues in an anonymous manner, whether or not they are linked, whether or not the key is kept.

I think that is one of the most fundamental statements that you've made about this whole process.

That deals with the current tissues and that can deal with the issue of how the tissue was actually collected, it seems to me. I think it would be a significant advance that could help change how things are done or could be done with current samples.

CHAIRMAN MURRAY: Would you let me talk about the thing I scribbled up there a while a go, because it's a little cryptic, I'm sure. Going back to the presentation that Mark made, and I argued that -- I asserted that it was a prior question, namely, might there be any particular relevance that we'd want to at least anticipate the possibility of going back to the patient about, with all of Mark's stuff being on the right and the answer to that question being, no, there isn't. But I want to ask a question about that as well.

If you answer yes, then we have to address the question, will we walk back through this wall and what kind of safeguards will we have, will they be procedural safeguards, will it be an IRB or another different body, whatever. We were talking about that a while ago. We will need to return to this and make

some recommendations.

I had some questions about the no option and the strategy Mark was outlining. He was proposing that there be this code and the code be retained. I have reservations about the wisdom of that.

DR. MIIKE: Except that unless you can answer the question, is it clinically relevant up front, you cannot have a yes if you don't retain them.

CHAIRMAN MURRAY: I think you have to ask. Well, this is a possible strategy. You ask the question, you're given an honest answer. There has to be some accountable procedure for ascertaining that the answer given is an honest answer. You're right, maybe one or the other of this is an empty set. I don't know.

MR. HOLTZMAN: Well, the impetus for maintaining the code, forget clinical relevance, is to be able to add additional information --

CHAIRMAN MURRAY: Exactly. Exactly. But I'm not sure you need to do that. There are schemes, encryption schemes, that actually lose enough information that you can't go back and figure out who

it was. But if you take that person's medical record, you can reduce again and end up with the same code at the end and you can plug it into the research data base. So it's a one-way loss of information that would permit --

DR. EMANUEL: It's not necessarily lost, but it is an encryption possibility. You're looking puzzled.

MR. HOLTZMAN: I'm looking puzzled because it has seemed to me that if there is a connection in one direction, by definition there has to be the possibility of a connection back the other way.

DR. EMANUEL: But that actually turns out -- I mean, again, I think it might be helpful to get an encryption expert here, but I think actually that turns out not to be the case. That's how this encryption system works so that I can send you a message that you can decode, but it turns out no one else can decode, and I can't decode either.

MS. KRAMER: If it's difficult enough, then it's not going to happen by accident. It's going to happen because somebody deliberately sets out and goes

to a lot of trouble to do it. That seems to me to be a rather extensive form of paranoia. No?

MR. HOLTZMAN: Again, let's come back to what we're thinking of here. The flow of information, the continuous flow to update the sample with relevant information is something we want to keep happening. So you're not going to set up a scheme where that's difficult. All right. We have said that we want the go-back to be as difficult as possible. We've said in the limited case, we don't want it to be possible at all.

DR. EMANUEL: Right.

MR. HOLTZMAN: But if you want it to be possible, it's for the limiting case of when there's medically relevant information that could help the individual where you would have a sufficient reason to climb over whatever difficulties were imposed.

So I think what Tom was raising is whether, if it's contemplated that a medically relevant result is unlikely, you should effectively break the connection back, the possibility of the breaking of the connection back. I'm willing to -- but I don't know enough to

assert that if you've got a connection in one direction, by definition you have to have the possibility of getting back.

MS. KRAMER: But the other aspect is that you're judging now what might be relevant down the line, which is not foreseeable.

DR. GREIDER: Right. Can you ever know what's clinically relevant in the future?

MS. KRAMER: No. Right.

DR. COX: That's one point. Another point, Tom, is that it turns out when people actually try and do this, there's a reason why most of these samples have identifiers with them, because you'd have to, like, go through hoops to get samples that don't have identifiers on them. To collect things in a truly anonymous fashion is like a serious --

CHAIRMAN MURRAY: Or uncollected.

DR. COX: Or even to have them in an anonymous fashion, to strip the identifiers, is not straightforward. It seems straightforward.

CHAIRMAN MURRAY: But we're hearing from Mark that it's not such a -- he didn't say it was a trivial

task, but it --

DR. COX: But the fact that most people don't have it stripped, I guess --

CHAIRMAN MURRAY: Well, wait a minute, David. I want to make this distinction between sort of the guardian of the tissues, and they have identifiers with them, right?

DR. COX: Right. Absolutely.

CHAIRMAN MURRAY: Now we're talking about the researcher who now petitions the guardian to get these tissues, through the wall, the stripping takes place before they get passed through the wall.

DR. COX: Yes.

CHAIRMAN MURRAY: That doesn't sound like such a difficult process to me.

DR. PITLICK: If somebody cuts off some new sections off the microtome --

MR. HOLTZMAN: We get samples every day from our clinical collaborators. We cannot tie those samples to an individual, and we get updated clinical information with respect to them as --

DR. COX: Right. But most samples aren't that

way right now, right, Elisa?

DR. EISEMAN: Well, it depends on what you're talking about. The samples that are sitting in pathology departments are identified, but when those samples leave pathology departments and go to the researcher, in most cases they've been stripped.

DR. COX: So even the pathologist couldn't get back.

MR. HOLTZMAN: No. They're not stripped, it's just that you don't have the connection --

DR. COX: But what Tom is saying is, one wouldn't be able to do that.

MR. HOLTZMAN: Wouldn't be able to do what?

DR. COX: Would not be able to go back. The researcher would not be able to get additional information that way.

CHAIRMAN MURRAY: The researcher would not be able to go back in and inform the pathology lab that -- this sample, which the lab could then break the code and say it was Tom Murray's sample.

DR. GREIDER: So instead of being recoded they would be uncoded. They would be completely stripped.

DR. EMANUEL: No. Or they would have a reduced coding so that you could still put, potentially, more clinical information forward, you just couldn't go back and figure out who it belonged to. This could be done. Now, maybe it's not practical, I don't know. But it's clear it can be done.

MR. HOLTZMAN: I think it's pretty easy, actually.

DR. PITLICK: Where can we get an encryption person to --

DR. EMANUEL: Yes. Again, I've put the scenario to someone I know, and it's pretty easy, according to him. But he may not have understood it fully.

MR. HOLTZMAN: Even with new information coming to the sample.

DR. EMANUEL: Yes. Yes. I mean, this is thing that has the FBI all nervous about it. I mean, that's what they're all worried about on the Internet, because they won't have the key. Actually, no one has the key. That's what the great thing about these

encryption systems is, no one has the key. You have a tag to it that only the person with the other tag -- but it turns out you can't even unencrypt your own message.

DR. PITLICK: Do we need more information about how often information would come from the other side of the fire wall to the researcher anyway?

DR. EMANUEL: Well, I think we have to presume that -- I mean, from what I've heard, a lot of people want to have that kind of a thing.

DR. PITLICK: But does it happen? How long do the samples stay around, if they're doing the research, that it would get updated anyway? I mean, it seems to me it might even be a rare event.

MR. HOLTZMAN: No. You're doing a cancer study and I'm looking at a marker for that. You want to know what happens to that patient six months from now, a year from now. They took this blood, and what happened to them, et cetera, et cetera. I may not need more sample.

DR. PITLICK: Well, I know. Okay. But you're going to keep it going that long rather than asking for

something, a sample from two years ago, and you have that information already in the record that comes to you.

DR. EMANUEL: Both kinds of research get done.

DR. PITLICK: I think it might be a relatively rare event.

DR. COX: I don't think so.

DR. PITLICK: You don't think so.

## NEXT STEPS

DR. MIIKE: Can I bring up something?

CHAIRMAN MURRAY: Yes. Then I want to turn to something else.

DR. MIIKE: If we're going to have any chance of a report ready in February, or even a buy-in by the whole committee, we've got to reach our conclusions and recommendations in December so that our January meeting is for the full discussion.

So we need at least a set of conclusions or recommendations for our December 9th meeting, however incomplete, so that we can see what's down there and argue over that and see what's missing.

DR. GREIDER: It's all up there. We just have to get through and define what we mean by all of those things, like what we did here.

DR. EMANUEL: You're right. You're right.

DR. MIIKE: I mean, it's just the mechanical table.

DR. COX: See, the reason I don't think it's up there is because I read this stuff, I really tried on the transcripts -- I mean, I wasn't here at the talk. Now I'm up to speed, but the words don't say it, I'll tell you that.

MS. KRAMER: You couldn't get it from the transcript.

DR. COX: I couldn't get it from the transcript.

DR. GREIDER: I have been here, and what I understand that table to mean, I think that everything we need to discuss is up there. It's very cryptic. We

have to go through each one of those things and define what we mean about each definition.

DR. MIIKE: But if we went to the full committee with that, we'd get nowhere. We would get absolutely nowhere.

DR. GREIDER: I agree, but it's a starting point.

MR. HOLTZMAN: Maybe the boxes represent all the key decisions, and Zeke has put a proposal together, right? So we have to have the rationale, first off, of why we've adopted this framework, where we've departed from generally accepted frameworks, why we've departed, if so, and then we need to decide within each of those boxes, do we agree --

DR. MIIKE: What I'm saying, though, is in order for the other committee to even understand what we're doing, we're going to have to say, what is the issue we're addressing.

MR. HOLTZMAN: Well, that's back to the conceptual framework.

DR. MIIKE: Framework. Exactly.

MS. KRAMER: Can I make a proposal? That when

we come into the next meeting that we ask Kathi to bring her computer and that we go through it box by box and spell it out in words.

DR. GREIDER: I think we have to do that before the next meeting.

MS. KRAMER: Before the next meeting.

DR. EMANUEL: I mean, here are blanks. You have blanks in your -- you know, the reason the blanks are given is because I think people should fill them in in their own mind as to what they want, and also try out the various different options.

DR. COX: Zeke, can I ask one question, because we're getting close to the end, just to help me with this. I can't imagine an identified community where there's not potential harms done in the context of the community. What's an example of that?

DR. EMANUEL: Well, the example I gave way back when was, you have the ongoing AIDS study of people that are already identified, and you want to take their sample. You collected blood, but you're using it up too fast and you want to make immortal cells. Okay. That's one example. In some other

examples, you might be looking at a gene that doesn't seem to carry any stigmatization for it.

DR. GREIDER: So I'd give the example of, you know, people who have attached earlobes versus non-attached earlobes, and you happen to have a large genetic population you're looking at and you want to ask, what is the prevalency of attached versus non-attached, what stigmatization is there to your earlobes?

DR. EMANUEL: Or baldness.

DR. GREIDER: Baldness. Okay.

DR. EMANUEL: We're talking about harms that are going to arise. That may be something someone doesn't like.

MR. HOLTZMAN: Then as a result of the discussion, one person's stigma is another person's beauty. I think that Zeke came forward with the recommendation that one ought to at least go to an IRB and ask the question, am I off the wall in thinking that there is no stigmatization.

DR. COX: But what you're doing is you're talking about things that cut across different groups,

so it's not unique to this group but it's present in a whole variety of other groups, too. So that makes it not be group.

DR. EMANUEL: No, no, no. It might be, you want to look, for example, at the baldness gene in a particular subpopulation, right? Or the need for eyeglasses.

DR. MIIKE: We have been so immersed in the details of our particular charge here that I'm not sure we are all on the same page about what we're supposed to be addressing.

So I think we've got to have something that's not condensed so much like this in terms of very specific options in very specific areas, but sort of, again, say something that's a narrative that everybody can relate to --

DR. COX: That's what I meant by the whole picture. I mean, that's what I said to Tom I'd try and write down. We can use this too, but if you have written down -- if each of us writes down what the whole picture is, it doesn't have to be 20 pages of text, but it could be an outline of what are these

global points that you're talking about, the issues that we're working on. I mean, this part is written down. Then you have both parts.

CHAIRMAN MURRAY: Let me ask if this would be a sensible way to go about organizing the next meeting on December 9. We have this schema in the various boxes and, I agree, a substantial part of the meeting should be to go through it and see whether it captures what we think is important.

We have a few other things that are mentioned there, I think, but we haven't fleshed out and will require some additional work.

One of them would be what kind of consent, when, in what form; second would be the circumstances under which you would want to walk back when you determine clinical relevance; third would be defining terms. I don't think we should do that at the meeting, we should do that before the meeting.

A fourth would be the whole issue of community consultation and/or consent. We haven't really talked about that much today, at my request, because Bernie is not here.

What other things? I would like to sort of block out a meeting where those become our agenda items. I welcome our contractors here, but it's basically going to be commission working with commission to try to make this --

DR. GREIDER: Well, we need to have in there why we collapsed clinical and research on the previously existing samples.

CHAIRMAN MURRAY: I think that needs to be in the report that we submit, but I don't think we need to talk about it, unless you feel the need to talk about it.

DR. GREIDER: I don't feel the need to talk about it.

CHAIRMAN MURRAY: Bette?

MS. KRAMER: Do we need to identify illustrative cases or illustrative scenarios to go with each of these?

DR. GREIDER: I think we should have to have that in the report.

MS. KRAMER: We need it in the report. So shall we just agree, as we go through it next time, on

what cases we want to use to make sure we've captured all these things that we keep talking about?

DR. EMANUEL: I've submitted some of those papers, and maybe other people in the course of time have others.

CHAIRMAN MURRAY: I think it would be helpful to be able to say that this case belongs in this box, and I think we should make that something that we try to do as we go through this.

MS. KRAMER: Perhaps we don't need to use specific cases, perhaps we just use general -- okay.

DR. MIIKE: I think it would be real useful, when we propose a particular policy, that we completely illustrate it.

MS. KRAMER: Right.

DR. MIIKE: Otherwise people won't really be sure what we're talking about.

MS. KRAMER: Okay.

CHAIRMAN MURRAY: What other things are absolutely urgent and must be on the agenda for the next meeting? Everybody is tired. If you think of something, call or e-mail me immediately, because we're

going to have to set the agenda for the December 9th meeting within the next few days. We can be flexible when we get here, but we do have to put an agenda out.

MS. KRAMER: Okay. Jumping ahead, and perhaps I was remiss in not bringing this up at the joint meeting, but thinking ahead to when we -- I'll speak for myself. Thinking ahead to when I have to pass on the work or the proposed reports of the other commission, I know I am going to be really loathe to do that without having heard not just their recommendations, but a lot of their backup.

I haven't read the material and I doubt I'm going to get to it. I mean, perhaps if somebody said to me, read papers 1, 2 and 3, they're the ones you need to, I could. But I'm not going to read the transcripts, I can't read all the material.

So I'm anticipating that the same thing is going to happen on the part of that committee, certain members of it, with regard to our report. If we want our report to go out in February, I can't see how -- it seems to me we're going to need the entire agenda of that January meeting to get that report by the full

commission.

CHAIRMAN MURRAY: Let's see where we are in December. If we feel like we have a set of recommendations that we are prepared to go forward with, then we'll just elbow and see if we can get most of the time in January. It depends also on where the --

DR. EMANUEL: But it also sounds like they're not going to be ready in January. I mean, that was what they suggested.

CHAIRMAN MURRAY: They may not. And we might be.

MS. KRAMER: But, you know, perhaps maybe you ought to explore that with Jim and Harold, or something like that. I mean, maybe that meeting needs to be expanded to a day and a half, something like that.

I went home from the last meeting, and I think I'm going to go away from this meeting as well, feeling that if we could come back tomorrow and put in another half day, that we could really wrap up a lot of stuff.

DR. MIIKE: You know, they're coming out with two reports.

CHAIRMAN MURRAY: Yes.

DR. MIIKE: One of them is so archaic, I have no idea --

MS. KRAMER: Right.

CHAIRMAN MURRAY: Right. I mean, Bette's targets are right on target. I mean, I think we already have a preview of the way different members of the other subcommittee are going to -- our report.

MS. KRAMER: And you know, Tom, I don't fault them because we may very well be in that position.

DR. MIIKE: This may be very well -- I mean, we were lucky in the cloning, there were no dissenting opinions or people bent on having an expanded personal opinion attached to this. I'm sure that --

CHAIRMAN MURRAY: It's going to happen.

DR. MIIKE: -- in our coming ones, that's going to happen.

CHAIRMAN MURRAY: No, I'm not sure of that. I think people are going to have to make a choice to what extent they want to get every single last line or consent of theirs exhaustively addressed and how much work we do.

MS. KRAMER: But there's another reason for questioning as well, and that is, because once that report comes out, if the press contacts anybody and says, well, what did you mean in that report, what are you going to say; well, I don't know, I wasn't on that committee? Well, you signed it.

DR. MIIKE: I propose -- telling them that.

MS. KRAMER: Well, fine. Okay.

CHAIRMAN MURRAY: But it depends. I would also feel comfortable in saying that I signed that because I agreed with the conclusions and the rationales, but the people who worked most on it were the people from the Human Subjects Committee.

MS. KRAMER: Okay.

CHAIRMAN MURRAY: I would have no problem saying that.

MR. HOLTZMAN: In terms of the writing of the report, if we're looking at a certain date and starting to look backwards, where do you need to be when, and are there things you feel you can start on already, or not? I think to the extent we can be helpful in you sort of doing the backwards -- chart --

DR. HANNA: I think probably at this point, and I apologize, I had to run over to the other subcommittee to hear a presentation so I don't know what you just went through, but I'm assuming that --

MR. HOLTZMAN: We voted you'd have the draft by the Friday after Thanksgiving.

(Laughter)

DR. HANNA: I think I have a sense of where you're going. I'm assuming that what you're saying is that at your December meeting you're actually going to try and do a straw vote of sorts, or at least get a sense of what your recommendations are.

So what I can be doing in the meantime is going through all of the materials you have, your commission papers, and trying to indicate what is coming out of those that is supportive --

DR. GREIDER: But it's not just the commission papers, but also the transcripts, because a lot of the stuff that we've been talking about, like that --

DR. HANNA: Oh, absolutely. I mean, we all know that the commission papers are going to be published separately in a separate volume.

DR. GREIDER: Right.

DR. HANNA: But there's material in there you want to include, or I'm assuming you want to include in the report. So I think in the next few weeks before you reconvene, that's the best I can do, and start thinking about drafting your framework as an explanation of how you're going to maybe -- that's the one thing I can get started on.

DR. GREIDER: That would be great.

DR. HANNA: It's just by working with Zeke's tables and boxes and try and turn that into text.

DR. EMANUEL: That may actually be most helpful for us before the December meeting.

DR. HANNA: I'll have to find out how quickly the transcripts are going to be available from this meeting.

DR. COX: And it doesn't mean just deleting the lines and leaving it that way.

(Laughter)

DR. HANNA: Larry, that's an old OTA trick.

(Laughter)

CHAIRMAN MURRAY: It's 3:30 and people have to

get their taxis, myself included.

Are there any urgent last matters?

DR. EMANUEL: I second the motion that we have as much pre-time to hash this out.

CHAIRMAN MURRAY: It should all be. I mean, we're not going to have any paper reports, as far as I'm concerned. It's going to be talking about the issues. If you have any thoughts about how to structure this, do we need half the data to do this, are there two or three other urgent issues, please let me know preferably by Tuesday. So think about it.

MR. HOLTZMAN: Kathi, could you re-send out the table of contents for the report?

DR. MIIKE: The 9th meeting is going to be solely genetics, right, because the other people are meeting on a separate --

CHAIRMAN MURRAY: That's right. That's right. We've invited them, and I hope many of them come. But --

DR. MIIKE: Just to observe, not to --

(Laughter)

CHAIRMAN MURRAY: To take note of our

brilliance.

MS. KRAMER: Tom, maybe you ought to send out a notice to the other commissioners that, for those with a particular concern about our upcoming report, would they please make an effort to come.

CHAIRMAN MURRAY: I thought I said that.

MS. KRAMER: Okay.

CHAIRMAN MURRAY: The meeting is adjourned.

(Whereupon, at 3:30 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the foregoing proceedings of a meeting of the National Bioethics Advisory Commission, Genetics Subcommittee, held on November 23, 1997, were transcribed as herein appears, and this is the original of transcript thereof.

SONIA GONZALES
Court Reporter