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DR. SHAPIRO: I have just been informed Dr. Childress has been called to the phone, but he'll be back here in a few moments. But we are going to, again, move some of our agenda forward. Dr. Mary Claire King is here, and she is going to speak to us on genetic research, individuals, families, and communities. And, really, we couldn't have anyone better do that, and a more experienced understanding in this area, a very distinguished professor of medicine and genetics at the University of Washington, and well known from so many things, I won't take time to enumerate them all, if you will forgive me. But it's a real pleasure to have you. We are very honored that you took the time to come down here to share some of your thoughts with us. Thank you very much for being here, and thank you also for all of the work you've done over the years that's so relevant to so many people. But welcome, it's very nice to have you.

DR. KING: Thanks very much, Harold. I have to tell you all something that only Harold and I know, and that's the real reason he's ever heard of me at all is that my brother graduated from Princeton and has been a royal alum for many years. And Paul was in the last of the classes which were male only. And since he's my younger brother. . . .

DR. SHAPIRO: Don't hold that against him.

DR. KING: I didn't go to Princeton. Had you reformed a bit earlier, I would be an alum myself.

DR. SHAPIRO: All right. This meeting is full of tragedies.

DR. KING: Perhaps, mine as well. It's both a privilege and daunting to speak to the Committee, because I'm very much like one of those children who moves to town when the semester is well underway. You all have addressed every issue I could probably bring up. And in many ways there is no wisdom I, as one individual, can add to what you haven't already discussed. What I thought I would do is tell you from our experiences that go back to 1974, three different studies that we've been involved in all happen to be breast cancer studies. Because, of course, that's a major interest of mine. And in each of these studies, which are quite different from each other, just name some of the issues that have arisen and how we dealt with them, and where we see problems, and where we see opportunities, and so on. But let me start by stating my premise of where we've come from philosophically in just a few sentences. First, that to some degree scientific evidence to the contrary, notwithstanding, the questions of genetics, genotype, and genetic identification are, in my view, different from those of any other medical problem. The

parallels with HIV are real, but the differences are real, as well. The parallels with any other concern for privacy are real. The differences are real as well. There are I think two fundamental reasons for it, which are human and not scientific. The first is that everything that is genetic has implications for our children, and nothing is any more important to any of us than that. And, second, that an enormous amount of murder has been committed in the name of genetics, and we would be extremely naive to believe that that's finished. Our human rights work in the former Yugoslavia now is like dramatic evidence that even though we are working with three populations of people, which, when you overlay their genotype are indistinguishable, nevertheless are engaged in patricide against each other of scientific evidence, to the contrary, notwithstanding. So, I take enormously seriously the work that you've set for yourselves. I consider it a blessing that you are doing it. It's not fun. It's not easy, and thank you very much for spending the hundreds and hundreds of hours you're spending on the problem. So let me tell you a little bit of our experience, and then just reflect with you on what it means and what use it might be to you. First, our project with families with multiple cases of breast cancer, a project that led over a couple of decades to identification of two genes which are responsible for inherited predisposition to breast cancer. In this project, we were workingXwe were and are working with very large families in which breast cancer and ovarian cancer are extremely common. The work began in the era before even DNA analysis could be done. And, of course, proceeded into the era of DNA analysis and was dramatically shot forward by the development of PCR. From the time of the invention of PCR, the availability of sources of DNA from persons who had died of the conditions of concern to us, that is, from people who were in the original generations of these families and had died of breast cancer decades before became critically important. BRCA-1 could not have been mapped, let alone found, without the use of specimens from pathologic materials from individuals who had died of this disease long before our project was ever undertaken. It was also, of course, essential that we know, specifically, who each sample belonged to. It's not a question of an optimizing sample, such as a matter of it being terribly important that we have my grandmother's biopsy specimen, in order to obtain DNA, both from the normal cells and from the tumor cells, and to work with both. The way that we addressed this question was to ask the next of kin of the persons who had died, if we could work with the pathology specimens from their deceased relatives. Sometimes that was a widower; very frequently, it was a child. This offered us no difficulties. We carried out that work. We kept the names attached to the specimens as we were working through them. We talked to people about their relatives directly. It was

very open communication. Of course, when we published pedigrees we were and are very careful to publish pedigrees in such a way that people who are still unaffected and young do not have their genotypes identified. They are simply excluded from pedigrees. But there is no question that we worked, and continue to work, with specimens from persons who, themselves, are in no position to be able to give us informed consent, because they have died and are never heard about. And those specimens are critical to gene-finding activities. So this is really an example, this first class of studies, of studies that involve retrospective materials, stored specimens with known people, where we do get permission from next of kin. The second kind of studies is exemplified best by our New York Breast Cancer Project, which is a project that Joan Marks and I are undertaking with now 12 institutions in the Greater New York area. This is a study of breast cancer among women of Jewish ancestry, who are breast cancer patients. It has really two goals. The first is to understand what the actual risks associated with BRCA-1 and BRCA-2 are; and the second is to understand if those risks are in any way modified by other genes, or by environmental exposures, or beneficent life events. The design of the study, to tell you just real briefly, so you'll see where we're coming from, is that every woman who is diagnosed with primary breast cancer in any of these institutions from 1994 to the present, regardless of her age at diagnosis, and regardless of her family history, is asked to participate if she self-identifies as Jewish. It is entirely self-identification. If she says, "Yes, I'm Jewish, and, yes, I had invasive breast cancer." Then she's asked to participate in the study. This is done through a stepwide genetic counseling process, which incorporates genetic counselors, who are the genetic counselors of their institution. So, it is a formal clinical genetic counseling process. She gives a blood sample. We genotype that sample first for three agent BRCA-1 and 2 mutations that are found in Jewish families. And ifXI won't get into the question of what about people who are negative, but from high-risk families. That's another project entirely. But if, for this project, if this personXthis patient has one of these three mutations, she then becomes the index case for a family, her family, and we work with her to trace the genealogy of the mutation in the family, regardless of the cancer status of the persons with that mutation, in order to obtain rigorous properly ascertained estimates by age of risk of breast cancer and ovarian cancer associated with mutations, and the interaction with potential environmental factors that I've told you about. Any person in this project who wishes genetic information back for themselves receives it and receives it with pretest counseling and posttest counseling, and no one is involved in the project until they have agreed and had pretest counseling. It is about 95 percent counseling, and about a 5 percent genetic analysis, so it's going along.

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As you might imagine, it's elicited a lot of interest in the New York medical world, and in the New York Jewish world. And, oh, sometime last year, some staff members of Hadassah became particularly concerned about this project, and I think some others. The exact history of what theirXthe origins of their concern elude me a little. But a consequence of their concern is that a fascinating meeting was held, sponsored by Jewish organizations in New York with senior officials of our NIH. Rick Cosner was there. Francis Collins was there. I suspect others as well. I did not attend. I was not invited, as it happened. But many of our clinical colleagues did attend. And the American Jewish Congress in the person of Lois Waldman, who is a lawyer, who works with American Jewish Congress, prepared a statement about genetic diseases in the Jewish community, which I've just received from Lois, and have consequently distributed to you. A number of us were asked if we were interested in signing the statement, and I very enthusiastically did so. So, my name is checked down here. To make a complex story short, I believe that the denouement of this experience was the following: That stigmatization, the possibility of stigmatization was directly confronted in discussion and was acknowledged as a real and legitimate concern. But that there was passion for not stopping biomedical research as a consequence of that concern. And there was, in particular, great concern that informed consent be individual, that every person have the right to either participate or not participate in a study. And if they chose to participate, to either participate anonymously, or not anonymously, and that the individual's right to make that decision for herself or himself be retained. I'll point out just a couple of the relevant paragraphs to you. But, like I said, I refer you to Lois's statement in general. Her comment at the bottom of page six, "Throughout American history, Jews have insisted that they be dealt with as individuals, not as some corporate body as in medieval Europe," and so on. And then toward the end of her remarks, "Genetic researchers and members of the Jewish community should maintain an ongoing dialogue, so they each may be apprised of the others concerns about genetic research involving Jews. The Jewish community should support passage of legislation to correct loopholes in existing law banning genetic discrimination in health insurance, and also support bills to prohibit genetic discrimination in employment, and to protect the privacy of all medical records," and so on. Development of this project in New York passed through IRBs at all 12 of the institutions, with whom we work, and, of course, at the University of Washington. And the concerns raised there are very much the ones that your Committee has been dealing with; that is, the ability of the individual to make informed consent. Since this is a prospective study, many of the issues that we're dealing with today don't arise. However,

the same question that I just brought up, namely, the working with specimens from, for example, mothers of persons who have died, may come up in the future. So, it's not necessarily buffered from that entirely. Because of the unique issue of working with one of America's remarkable populations with a still coherent genetic ancestry, I have realized for myself early on that I needed to know a lot more about Jewish history in America. I am just parenthetically one of these persons who learned only as an adult, that she is in fact partly Jewish. Madeline Albright is not alone. It turns out my mother was born a Cohen, and I learned that after my daughter was born. American history is full of these stories as well. What we decided to do, in order to educate ourselves was to establish before we began the project an advisory committee, not an IRB, but an advisory committee to educate us about what weXand by we I mean Joan Marks, and the oncologists, and the clinical geneticists, and the counselors, and I thought of as the critical kinds of issues that were likely to arise from our participants. Stated socially, what does it mean to be a Jew in America? What does it mean to be a child of persons who were survivors of the Holocaust? What does it mean to be both an Israeli citizen and an American citizen? What about our collaboration with our Israeli colleagues? I haven't discussed that, but we have an exactly parallel study going on in Israel by a collaborative group there. And this committee meets about once a year. And, importantly, has undertaken education of genetic counselors in New York about those issues. So, it's been for me an enormously enriching experience to have that committee involved. They have not been a hoop through which we needed to jump. They haven't had any veto power over the study at all. They never asked for that, and that was not the purpose. But they have been enormously helpful in suggesting how to do it right. There has been mutual respect and we're learning a great deal. The third project I want to discuss is, yet, again, different. This is a project which is just now getting under way. It's our collaboration with the NSABP, and their tamoxifen prevention trial. As probably most of you know, the tamoxifen prevention study of the NSABP has just released its first results. The nature of this project was that women who were at high risk of breast cancer by dint of family history, or age, or personal threatening history, but not actually having ever been diagnosed with breast cancer were asked to volunteer for the project. And if they volunteered for the project anywhere between five and eight years ago, were randomized to either tamoxifen or placebo, were asked to remain on the regimen to which they were randomized for five years. And at the beginning of this study no one had breast cancer. Thirteen-thousand women volunteered for it, were randomized 50/50 into two groups, and the study proceeding forward triple-blind, with neither the women, nor the

physicians, nor the investigators knowing who was in which category until one committee, which consisted of only three statisticians, in evaluating the results reached a stopping rule, which had been previously defined on the basis of statistical grounds. So when the stopping rule was reached, that is, the stopping rule was either the tamoxifen would have a benefit that was significant at a preordained statistical level, or would have a detriment that was preordained at a statistical level. When that stopping rule was reached, the results were revealed. That happened, it happened earlier than they had anticipated. The results of the trial are that tamoxifenXthat the women who were randomized to tamoxifen have 40 percent fewer breast cancers than the women randomized to placebo. Concomitant with that, the women randomized to tamoxifen have higher risks of endometrial cancer, so this is not one of these entirely beneficent situations, and each woman needs to decide for herself. And that's a whole set of issues in itself. My interest in this for the last eight years has been whether women who would turn out to have inherited alleles predisposing them to breast cancer, would be particularly benefitted, or particularly not benefitted by taking tamoxifen. One could make the argument either way, depending on how one interprets biological roles with BRCA-1 and 2, which is hardly a settled matter either. So whatXthe study that my lab designed with the NSABP and the NCI is toXwell, I need to also tell you parenthetically that each woman at the time that she entered this study gave a blood sample and signed a consent saying that this sample could be used for investigation of biological markers. There was no specification to BRCA-1 and 2, because they weren't known yet. They weren't named by name. So, the study we designed from the purely design point-of-view, was to take the blood samples from all of the women among the 13,000 who had developed breast cancer. And about three women from the cohort, who had not developed breast cancer for each woman who had, so about a thousand samples in all. To genotype in my lab, all thousand of the DNA extracted from each of those blood samples all the way through BRCA-1 and all the way though BRCA-2, so as to determine who had mutations in those genes, and then to answer to questions. What is the absolute benefit or detriment associated with using tamoxifen if you are a mutation carrier? And what's the relative benefit or detriment? There, clearly, is not going to be a way to say this with any level of significance, but we will at least get some point estimates. The question, of course, arises, how does one do this? To what degree does one anonymize? I used to think anonymity was like pregnancy, but I now realize it is not like pregnancy, that there are degrees of anonymity. Right. So, we turned to the Participant Advisory Board of the tamoxifen or of the NSABP, and, in particular, of the tamoxifen trial, who are women who are on the

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trial, and discussed it with them. To take a couple of extremes: at one extreme, we would have attempted to go back to every one of 13,000 women and asked if we might put their name into a hopper to be randomized to being in the trial or not, and not have put their name into that hopper, unless we could obtain that consent. That was not feasible. As in any other large randomized trial, large numbers of people drop out. It was possible to follow people's ultimate cancer status through publicly available records. But something like 15 percent of people from each arm had dropped out, just as people do, and we wouldXexpense aside, we would have had a highly incomplete follow-up had we tried to go back to every woman and get explicit permission to use her sample, and we would have had a serious bias to the trial. So, I said I would ratherXI said to myself, “this is a deal breaker.” I would rather not do the trial after that. Also to take the opposite extreme, we would have tried to contact every woman and give back to her, her individual results. I also oppose that, as did the Participant Advisory Board, because the samples, although they were collected by sincere, extremely well-meaning investigators, were collected at hundreds of different hospitals. They weren't collected using clear guidelines. There is always the possibility of sample mix up. And while that's a detriment to a statistical analysis, it's devastating to an individual. So, if someone needs an individual result, they really have to do it properly with prospective collection of sample. So, we were really left with some intermediate possibilities. One was toXI'll tell you the two that we've struggled over. They start the same way. That is to put all names of allXwell, no, I'm leaving out a step. The women in the NSABP tamoxifen trial receive about four-times-a-year a newsletter. And we've been describing the intent of doing this genetic study for years now. And in the most recent newsletter, the study is described, and so that it will get under way. And in this most recent newsletter it says if you do not want the sample that you gave years ago to be used, send back the send-back card and we'll remove you from the randomization, and the time to send back that card isn't over yet. So, I don't know how many will get that. But, barring that, everybody's name goes into the randomization, and about a thousand names are pulled, including virtually all of the cases. Then the samples are taken from the freezers, and are taken to an independent laboratory, a clinical laboratory, where DNA is extracted, and the NSABP identification number is removed and a consecutive number, one to a thousand is put on the DNA. The DNA is given to me. Any extra DNA is returned with its original NSABP identification number to the original freezers. I never know who these individuals are. At the same time, the NSABP statisticians who have assigned these one to one thousand numbers extract from the enormous record of information on each person the critical pieces of information

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that they and we perceive that they're going to need. So, this is all material that's been obtained up to this moment. For example, do they have cancer or not? What year were they born, and so on? And that's put into a separate file with the consecutive number. We do the genotyping. We give the genotypic information back to the statisticians at NSABP, and together we do the analysis and we get an answer. The critical question then is, is the link between the identifier in NASABP, it's original identifierXwhich, of course, could then be traced back to the woman herself- and the consecutive number kept or destroyed. The way that this study now stands, and the way it's been passed by all of the IRBs, that link is destroyed. The reason we decided on that is that this committee hasn't finished its deliberations yet, and we don't know what your wisdom will be and we want to be conservative. The downside of this is that we will never be able to doX

DR. SHAPIRO: Say that one more time.

DR. KING: I said we don't know what your deliberations will yield. It's perfectly possible that your deliberations will lead to a recommendation that studies of this type be completely anonymized with no possibility of anyone ever getting back to the individual, which we will not now be able to do. And we don't want to put ourselves in conflict with this Committee at any time in the future. The downside is we will not ever be able to do the survival studies, and I am very concerned about that. The Participant Advisory Board is, if anything, more concerned than I, but it is the price we've paid. So those are three of our experiences, and those are where we stand. And I have no special wisdom that's what's up. I'd be happy to talk with you.

DR. SHAPIRO: Thank you very much for describing these studies, and this is not my area of expertise. But I really, and, nevertheless, must say I'm very impressed with the care that you've taken in proceeding in studying diseases in this particular community, and it sounds very impressiveXI'm sure to my colleagues as well. I have a bunch of questions, but let me see if other members of the Commission want to speak. Yes, Diane, then Bernie.

DR. SCOTT-JONES: Thank you very much. And I have a lot of questions, but I'll limit myself because I'm sure everyone else has questions for you as well. I was very impressed that it seemed that your learning about the Jewish community in your work was something you saw not as a burden, but as an interest in the population that you study. And I suppose that the ideal, and how we promote that through the variety of mechanisms that become available to us for promoting scientific standards and ethical standards probably promote just what we did.

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DR. KING: I think it's terribly important that the role of the citizen advisor, as educator, and the role of the IRB, as regulator, be separated. We need citizens on both, but I think they are different roles.

DR. SCOTT-JONES: Could you say more?

DR. KING: On our committee that Joan and I put togetherXanyone who knows Joan Marks, knows that for Joan Marks to put together a committee like this in New York, where there are people pounding on her door to be on it before it was over includes a psychiatrist, a historian of Holocaust studies, a journalist, no one medical. The other people are women who are philanthropists, and I don't know their original professional training. But everybody in the committee is Jewish, except me, then it turns out I am, too. I didn't know when we started all of this. So, anyway, what that committee does is educate us and help Joan, and to a lesser extent me, establish lectures, and seminars, and courses, which are required for the counselors who are involved in the project. That's teaching. That's not the same thing as our going to them as an IRB and saying we need your approval for this. It's a mutual teaching process. And I think itXI think it allows us, as scientists, to let our hair down, and to express our insecurities over these issues. I mean to take one very dramatic example. I said we haveXwe encounter almost no one who has inherited mutations who is elderly and has not yet had breast cancer, but there are a few. And one is a woman who is a Holocaust survivor. She since died, but she was alive last year. She's in her eighties. I said how is anybody going to talk to this woman about her experiences as a young woman? I mean this is beyondXcompletely beyond the experience of anyone, and we worked out a way to have this person interviewed with the help of a person for whom this was not beyond their experience. And I was able to admit completely freely my need for help in that area. That's very different than a regulatory process. So, teaching and regulation are both essential, but should be independent I think.

DR. LO: I, first, just want to thank you for a wonderful presentation and a lot of food for thought. Two questions for you about the tamoxifen study. The first has to do with deciding whether you can use someone's sample. Others have suggested that in a study like that where you really have a well-defined population and a participant advisory

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board that there be some sort of surrogates for individual consent since you have to have 95 percent of the people who you can contact that would agree their samples to be used. That gives you perhaps some ethical warrant to do more than the opt-out. So my first question is about your thoughts on the other options you could have employed. My second question, which I think really is directly in line with some of the issues we've debated, is how you handle the double coding at the NCI and then the code that's given to you with your thousand samples. At one point in our deliberations, we had talked about the status of the sample as the researcher has it which may be different from the status of the sample in the original repository. So as I understand it, the NCI can link everything...No, but it passes its use in a way that you can't link back to the original but they can feed you certain information. And what your case really illustrates is several things, but one is certainly the cost that you pay when you give up not being able to retrace that linkage. And let me elaborate what I think is the situation. I mean in breast cancer disease, you know it's a 20-year disease, and so whatever trends that were strong enough to prompt the stopping of tomoxofin are of marrying up the totally predictive of long-term trends. And so this is a disease where if there ever was a disease where you'd want to be able to walk back and get feedback at 10 years, 20 years, on the incidence of the cancer, this is one of those. So that's one thing, just that we keep in mind the cost of policies that are intended to enhance individual autonomy and things like that. But the second point is that we have also considered what may be in fact computer science fiction: but encryption schemes, where you continue to be blinded to the ultimate identity of the patients but you're able to get updates on the breast cancer status of the sample through the central registry as they get it from whatever cancer registry direct. So it seems to me it would be important to try and develop both the technology to do thatXwhat we've called sort of one-way communicationXboth to really look seriously at the technical ways of doing that and still protect confidentiality, but also to carve out the ethics of that because it seems to me your case is an example where my initial reaction is, let's try a way to protect those people who really don't want to know of, don't want to be bothered by recontacting, but somehow to also answer the very pressing scientific questions that you played out, which ultimately, I think, are really going to provide tremendous clinical benefit to people at risk for the devastating condition. So I think it is really going to help us to try and puzzle through this third case with you because it really touches on issues that we have struggled with. I guess my final point is that I guess it bothers me that because we haven't said whatever it is we're going to say, people are rather trusting their best judgment, it seems to me that everything we've heard and everything I know about your work is that I would trust you as an investigator with your colleagues

and your advisory boards to do the right thing in ethically perilous territory. I think there's a cost to the perception that until we've made a decision, investigators take the most "conservative approach," but it's conservative from a certain point of view, it's very wasteful from another point of view. And I think that's something we have to...I mean colleagues of mine have expressed their concern at our not making some sort of statement, which then may or may not get picked up as policy, but I think your case really drives it home that our not acting in a timely way is having a real impact that's not going to be reversible on studies that I think anyone would say are really important, significant vital signs that need to be touched.

DR. KING: That's exactly right. The...it's not scientifically or medically justifiable to do what we are doing because we will not be able to answer the question if a woman develops breast cancer and had an inherited predisposition and was on tomoxofin, is she best advised to have another round of tomoxofin, to stay off it, is her chance of recurrence less because she's already been on it. We won't get any of the that information about people with inherited predisposition because we won't be able to follow them up. The way our coding scheme works is thatXthe way it's set up to work right nowXis that the NSAPB statisticians who are the people who actually do the analysisXwho, incidentally, are superbXwill make the file of the basic clinical outcomes as they now stand and the basic demographics that they need. They'll put that file in place. Then that file will have numbers attached to it, which will be the same numbers that will be given to the clinical laboratory who is doing the DNA extraction, and then the link will be broken. I will get the DNA samples with only numbers one to a thousand on them, and by that time that's all that will be on the file that the statisticians will have, so none of us will have the linkers. The material from the clinical laboratory will go back to the repository with the original numbers on it, but those numbers will no longer have been physically on the same tubes with the one to one thousand on them so nobody, short of reverse genetics and sequencing the entire gene of the sample, nobody would ever be able to go back. There are ways-and the statisticians developed one when we were more optimistic about being able to do follow-up for clinical outcomeXof doing encryption so that I, as the geneticist, don't ever learn who these people are. I don't need to know that. However, there is no way you can have clinical outcome and not have some human being know what all the information is on that person, someone has to be able to know. Now, bearing in mind that these are people who are caring for these patients, it is an extreme position to take to say they don't have the right to have any of this information, but that's what we've said. To go back to the surrogates versus the opting-out strategy, again, we

took the most constrained route. It has added, oh probably, eight months to getting the study started, and it's added a great deal of cost. In this case, the NCI was prepared to sponsor that cost so we were all right. It has had, I think, real costs in public health costs because when we decided on the opt-out strategy rather than the surrogate strategy, none of us thought that the results of the trial were going to be coming online so quickly. And consequently, we thought we had a little bit more time to play with. The reality is I still don't have those samples in hand. It's going to take me a year to 18 months to do all this genotyping and I haven't even been able to start yet, and I've been talking like this since 1990. So this is not a good example of getting something done in an efficient way, and yet, everybody involved knows what they're doing. So there's got to be a better way, right?

MS. CHARO: I always hoped this Commission would have an impact, this is not the one I'd hoped it would have. Mary Claire, if I understood the protocol correctly with regard to situation number three, the tomoxofin study, the only thing that you would have had to do differently in order to be able to retain those code links and get all the follow-up that you want, and still be in compliance with the federal regulations, the only thing you would have had to do is to have sought consent as opposed to simply having an opt-out provision. You were already mailing to people at known addresses, and you chose to mail out something saying if you don't want to be in here, mail this back. If all you had done was to mail something out that said, Would you be willing to participate, you could in fact have kept all those links under the federal regs, no problem. You would have met every requirement. And since up until now, as of now, the discussion on this Commission has been really about how to enhance enforcement, appropriate enforcement of those existing regs, it seems particularly tragic you would have destroyed those links. I'm asking how much more expense, how much more delay, how much more sample size reduction do you think you would have had if you had taken that last step in order to uncomplicate your lives and allow yourself to get the updated info?

DR. KING: It's a scientific problem, and naturally we discussed it. The difficultly is that the people that you lose by an opt-in strategy are not a random sample of the group as a whole. For example, you lose all the women who died of breast cancer. And you also lose all the women were lost to follow-up for the trial. And that's a lot of people and they are not random. If they were random, it wouldn't change your point estimate, but we did simulations on how much nonrandomness/randomness in order for us to follow up,

rather, for death or other reasons we could sustain and still have a meaningful response, and decided it was potentially devastating to the results, that we couldn't maintain the statistical rigor.

MS. CHARO: Just a clarification on this, if I may? For those who died, their samples could be used without any kind of consent because they're not considered to be subjects under the regs and you're allowed to use their stuff with impunity. The question being, could you know who those people were so you'd be able to pull the samples out of those people who are now dead and say, fine, these are okay, and add them to the samples of the people who'd opted in. So, in fact, it would have been...it might have been possible if you can identify them to have gotten at least that subset of nonconsenters back into your sample, leaving only those who actively, who failed to consent and are still living. Either lost to follow-up or genuinely failing now.

DR. KING: Right.

MS. CHARO: Earlier today, Diane was talking about some of the challenges of statistical validity that always exist in study design and I'm now getting interested in understanding exactly how significant this problem is as compared to the general problem of validity that Diane talked about because the current regs, if the current regs have this high a price, we should be very much aware of it.

DR. KING: This, of course, is the world I come from, and it doesn't take very much ascertainment by us to throw point estimates off drastically. I think had it been only a matter of the decedents we could have dealt with it. The greater difficulty is that when everyone asks 13,000 people to send back a card saying they're opting in, your response is very, very low. And the cost of going back and back and back and back and getting that up to 80 percent, let alone higher than that, is extremely high.

Then you have to prove to your own satisfaction that the people who haven't responded are not biased in one way or another. It's ... it was the statisticians that basically drew the line. We did a little pilot and the response in sending back the card to the pilot was something like 30 percent, 70 percent nonresponse.

MS. CHARO: And this was with highly motivated, educated, newslettered people.

DR. KING: Oh, terrific people, newslettered people. Basically they're probably newslettered to death, but what can I say? And it wasn't that they weren't interested. I mean you follow up with this little pilot and you say why didn't you do this, and they say, oh, but you already have my sample, of course you can use it, oh geez, did I not send it

back? It's a big study. And it's a sort of a specimen of these large trials that one will need to confront.

DR. SHAPIRO: Other questions? Let me go back to something you said right at the very beginning in dealing with genetic information, and your own view as to why it's different from other kinds of information. At least as I recall, one thing you mentioned was that it had implications for one's children and so on downstream. And the other I wasn't quite sure that I understood what you said. It sounded to me like you were saying this kind of information's been misused in a serious way, very often in a historical sense, or be used for...I didn't quite understand. I mean I understand what's going on in the former Yugoslavia, but I didn't quite understand how that related to genetic information.

DR. KING: I think the point I was trying to make is not that legitimate genetics has been used that way, but that all of our concerns, just as citizens, not as scientists, about the way that a stigmatization, racist arguments, and eugenic arguments have been used against people are real. No question about it. The fact that it has, the fact that one can use population genetics correctly to debunk those arguments is important. But it is not sufficient. It is not sufficient for me as a geneticist to be able to say look, there's nothing new here, this is all the same as it was before. There are too many historic counter-examples. So what I'm saying is that the problem is a historical one and not a problem with genetics itself. Does that help?

DR. SHAPIRO: Okay, no it's very helpful. Let me ask you about what I think was the second experiment, or second...well, it had to do in any case with the need when someone is deceased. You went to their next of kin. And I was trying to think here how you figured out who that was. They might have had two children, they might have ten children, they might have I don't know what. How did you figure...and what if they disagreed? Let's say there were just two children and they disagreed. How do you deal with issues like that?

DR. KING: Right. Typically the way families come to us is by self-referral or referral of a physician of one case. And we quickly become bonded with the family, with lots of people in the family. So very frequently next of kinXfor example, if a woman's mother has died and a father's long since deceased also we ask that woman for permission. We have not had the worst possible scenario in that, a situation in which there were, let's say, two daughters, and one said don't you dare look at my mother's

sample and the other one said I insist that you do. That hasn't happened. We have had a number of times a situation in which one daughter has said I want the study to proceed, I want our mother's sample to be used, and the other daughter has said I don't want to be part of this. And then, as you can see, we proceed. And the issue of intrafamily confidentiality is what becomes enormously important: the daughter that doesn't want to be part isn't part. I think what we would do...the scenario you bring up is analogous, I believe, to a scenario that has happened, a number of times, in which we know a woman's genotype, we know that she has a predisposing allele, and she doesn't want us to tell anyone in her family. Or in particular, she doesn't want us to tell a younger sister who is at risk, 50 percent risk, of inheriting the allele. And we are bound not to tell that younger sister. We work on it over months. That's why genetic counselors are trained the way they're trained. And we simply discuss the issue with the person and hope that in time the person will come around. I think, and so farXknock on woodXeach time that's happened they eventually have. There are all kinds of personal things that come into it; eventually each time it's worked. I think if we did confront the scenario you present we would do the same thing. We probably wouldn't use that sample until we had gotten past the unhappiness of the other sister. But we'd just keep talking to them. We're talking about real people here, and we have real relationships with them, and the relationship doesn't stop when we know their genotype.

DR. SHAPIRO: If you wereXand I apologize if I don't ask the next question in a coherent way, I'm not sure I have a coherent question, but there may be something hereXif you were trying to design a study which required genetic material from lots of members of the family, some of whom were deceased, and then going on a few more degrees in one way or another, and the question is for the deceased relatives, the deceased kin this case. There's some misunderstanding...there's some kind of ambiguity about current regulations, whether they are human subjects or not. On one hand they're not; on the other hand, they have information which impacts other people who are living and one could argue that they are. Our understanding of current practice is deceased is deceased, and this other issue is they're just not treated as human subjects for the purpose of the regulations. But the kinds of studies that you're concerned with and deal with, would it be a huge and superXnot be hugeXwould it be a significant barrier if you were told that if you want to use the material from deceased kin that you have to get permission, as you've mentioned next of kin, whoever the first living relative is with the oldest living relative, would that be a significant barrier, an irrelevant barrier, a big problem, small problem, if we began treating these deceased individuals in this sense as

kind of human subjects? When you consent of one form or another from their living relatives.

DR. KING: Are you referring to a situation in which I, as the investigator, need to retain the identification of the person?

DR. SHAPIRO: Yes, right.

DR. KING: Right, because for the anonymous case it doesn't matter.

DR. SHAPIRO: That doesn't matter.

DR. KING: Right. I think any, whenever anyone is working with real families, any regulation that sets any one policy in stone is probably asking for trouble. I think that...I have no problem at all in asking for a next-of-kin agreement. We've always done it, and I can't imagine that we wouldn't always continue to do it. It's simply a matter of showing respect. What I would find very burdensome and would probablyXI mean it would probably be a deal-breaker for me, I probably wouldn't do this work any longerXis if I really had to go to everyone in the family because that forces people into dynamics with each other which they may choose to avoid. And it destroys the privacy of the individual. And so I think this becomes one of those situations in which it's necessary that individual investigators and individual IRBs and individual genetic counselorsXwho are after all trained in this kind of thingXsee cases one-by-one, and when it makes sense to work with this daughter rather than this daughter that they be allowed to exercise that judgment. But that families be respected and that there be "a" next-of-kin permission granted. That in itself I don't find and anathema at all.

DR. COX: So, Mary Claire, I, too, would like to thank you very much for coming because you give a perspective of a person in the trenches who's thoughtful about this, that I think that oftentimes we don't get before the Commission. Having said that, though, I'd like to come back to this issue with respect to the bias in the sample from a scientific point of view because I'm having trouble with this. I'm not an epidemiologist and so I really am seeking clarification on this. Certainly I can envision that if you had only 30 percent of the sample it could be biased, but it might not be. And I don't have any idea for figuring out whether it is or not. On the other hand, doing an opt-out, even if only ten percent of the people that opt out, how does one know that those don't bias the sample? So I'm having trouble with the logic here.

DR. KING: Right. There's a huge statistical field devoted to this problem, right?

The way that one can determine whether one's opters-out are biased is that a personXthis all happens before there's any randomization at all into my studyXone's opters-out send back their cards and the statisticians can say, "Right, the people who are opting out are people who are over age 70." Right? And if it's something that simple, one says right, this project, therefore, is generalizable to people under age 70. If the people opting out are people with a family history, that poses something different in terms of genetic analysis. The relationship between multiple, independent variables influencing a trait and the degree of disproportionate opting out that one can sustain, and the consequences of that for point estimates are, as I said, a matter of statistical analysis for which there are protocols that one follows.

DR. COX: But that approach could really screw you, too, right? Because the people that choose to opt out could be very nonrandom and it would make it very difficult to use the study.

DR. KING: Right.

DR. COX: So I see that you could get screwed in either direction.

DR. KING: You could, in principle. However, in or experience with lots of different opting-out and opting-in pilot studies and real studies, asking people to opt in when the sample is very, very large is enormously expensive and fundamentally unwieldy. Opting out simply works better because there are far fewer people...people, if they don't want to be in a project, are much more willing to send in a card saying I don't want to be in a project than are people who are willing to opt in. I mean, I myself, as a subject, without realizing it when it was at Kaiser, of one of these opt-in studies, I forgot to send the card back. It's just something you have to remember to do.

DR. COX: So I understand that point. It's the point that you just made was an unwieldy one, but not a scientific one.

DR. KING: But it becomes scientific, David, because if only 30 percent of the people send a card back saying yes, I'll be part of the project, it would be remarkable. It would be testable and remarkable if those 30 percent were a random sample of the overall group. And chances are they won't be and you will lose your ability to work.

DR. COX: Because I just wanted to be very specific about this because there are several reasons not to do it. But you're saying in addition to the unwieldiness with very large samples, there's a scientific reason. So my final question on this is what's a very large

sample?

DR. KING: The interfamily studies, clearly we have an opt-in strategy, right? In our New York breast cancer study, we have an opt-in strategy. I think the...one draws the line depending basically on how much time one has before the issue becomes either devastating to the world, as in the case of AIDS, or moot as in the case of tomoxofin and breast cancer. Any amount of money that one has to do triple follow-up through the various waysXthrough mail, telephone, and personal visits of the people who don't send back cards. It is a very expensive thing to do a full-scale follow-up study. I mean it would be millions of dollars for a sample this large. So I can't give you a number that would apply to all studies. But I can tell you for the New York breast cancer study, numbers don't work, David, because it depends on where you are.

The New York breast cancer study, because that involves so much activity on the part of the participant, that is, if she wishes to know her results she has to go to pretest counseling and genotyping and post-test counseling. I am sure we are getting much, well we're getting a 60 to 70 percent assent to be in that study. I am concerned that the people we're losing are not random. I'm concerned that we're losing the elderly women, I know we are. I'm concerned that we may be losing people who have less family history. But I don't know any other way around it. So you have to use your brains; it's a balance of the scientific questions you're asking, the money you have to spend on it, the time you have to spend on it, and the actual risk to the real person that's involved.

DR. COX: That's very helpful, thank you.

DR. SHAPIRO: We have three or four commissioners who want to speak, and then we're going to have to move on to our next subject I'm afraid. But the four I have are Bette, Larry, Alta, and Bernie. And Diane, you want a last question also?

MS. KRAMER: Thank you very much for your presentation. I sit here as a public member and I've spoken with a couple of the other Commissioners informally earlier today because as I sat here this morning and I listened to the conversation, I have this very, very real concern that we are working so hard to eliminate risk from the research activity that we may be inviting an enormous cost to research activity and to what it promises for the public. And when we had mini-hearings back several months ago, we heard consistently from the people who participated that they, insofar as they represented the general public, that they were not really concerned about this. They were only concerned to the extent that they didn't want their insurance companies to get that

information. But aside from that, they had a commitment to the idea of research, they had a commitment to the notion that there's a public responsibility to participate since the public was going to be the beneficiary of the research. I'm curious, I have a couple of questions. In working with either the people who participated in your study or the advisory group, what kind of feedback did you get from them? Did you find that they, in fact, were worried about this? Or did you find that in fact that you who were doing the study were more concerned than they were?

And do you, in the last analysis, do you have anything to suggest to us that could help us as we try to strike a proper balance between protection and permission for the research to go forward?

DR. KING: My experience in all of my work, across all studies, not just these three, has been exactly the same as yours. This is all my breast cancer work. Participants have been very committed to the work, and participant advisory boards have been very committed to the work. They make remarks that are anywhere from slightly patronizing to quite caustic about the degree that we obsess over these things. I mean someone said, "Our tax dollars at work again?" Someone else said, "How many angels do you want to put on the heads on pins?" Somebody else said, "Wake me when it's over." However it's true that they see only one part of it, and they don't see the whole picture as you do. Surrogacy instead of opting out, let alone opting in, would be an enormous help. I honestly think opting in would kill the field. Opting out we can tolerate but it has costs, both financial and otherwise. Losing the ability to follow up has, as several of us have now said, has enormous medical and scientific costs. And if there is a way that we can maintain our ability to obtain critical follow-up information on people in large cohorts, it would be a tremendous help.

MS. CHARO: I find myself wondering a couple of things here. First, by destroying the links you actually eliminated the requirement to obtain even an opt-out. At that point you could have used the stuff with impunity, saved yourself the statistical challenges that David has described, and yet you chose not to, and I'm curious as to why. Second is, in light of your experience and your certainty that opting out is far... to allow you to use their stuff in the future, either with no further consenting process or with an opting out process, in other words allowing people to prospectively contract with you for a less onerous consenting process, as a way around this problem, at least prospectively.

DR. KING: Right. The prospective studies I'm involved with use very much what you described there at the end, a process in which the ... for example, we're working with the cohort from Kaiser of young adults with inherited...with a hearing loss, and we want to find out if it's inherited or not, and at this point we have no idea whether it will be or not, so it's going to be years in the future before we know. And it has this kind of tiered system.

To be blunt, the reason why we went through more hoops than seem reasonable is because there's a lot of confusion out there, there's a lot of concern out there that if we had not gone through all these hoops that the study would have to be shut down at some time in the future. The concern is in part from our colleagues who work inside the government and who are trying to do the best they can in a very uncertain situation. It's...I can't defend the logic of what we did. I can simply tell you that our goal is to try to get to women good information and not to be completely paralyzed in getting good information to them. And there were enough people, both from the intramural NCI and among us who were concerned that if we didn't do this in the most constrained way possible that we might have to shut the whole thing down later on. Your logic is indisputable.

DR. LO: Well, I'm still trying to understand this enormously complicated dilemma that you're facing. It seems to me there are a couple issues we haven't highlighted yet. One is the sort of rapidly changing HMO field. So when consent was first obtained in the Boston study, you asked for permission to use biological markers because that's...you didn't really know what they know. And one of the things we're going to have to deal with is samples that some consent was gotten in a meaningful way but you couldn't have anticipated what you were going to use it for. And somehow, is that different than samples where no consent was obtained or only general consent to sort of use it for research? I think we need to think about the grandparenting clause for samples where, you know, an honest attempt was made to get 1994-level detailed consent.

DR. KING: If you write in Shakespearean English, you shouldn't be precluded from now speaking about it in modern English.

DR. LO: Right. The second issue has to do with an appeals process, that you were faced with a situation, it seems to me, that what is behind the original CFR regs wasn't going to anticipate it. And rather than be forced into the situation of having as a matter of prudence to take the most conservative interpretation, it would have been desirable to have some working body that could have said, let's look at your situation as a special case

and see if, notwithstanding what the regulations say how they were interpreted, they really shouldn't apply to this situation because it's a different ethical situation.

And I guess I'm trying to find ways, because this is going to come up again no matter what this Commission recommends or what gets adopted as policy, whatever is 1998 standard consent for future uses, someone's going to come up with something next year or the year after that we really didn't specifically ask for. And are we going to face this problem again later where people are going to get a new type of study that has different risks and benefits and people will say, well you didn't really ask about that, you asked in such a vague way that who knows what this means.

DR. KING: I like your idea of an appeals process, and the woman who spoke just before lunch representing IRBs the world around might well have ... she and her organization might well have something to contribute to how to set up an ongoing appeals panel. It would have been a big help for us in this situation had something like that been in place.

DR. SCOTT-JONES: I would like to have you say a little bit more about what you're calling "opting in" as a process in your, what I thought was a very strong statement that opting in will kill the field. I was very impressed by your concern about the Jewish community and efforts that you're making to have ties with them, which I think is wonderful to have an ongoing relationship with the population, the community, that you're studying. But it seems that opting in, well what you're calling "opting out" is like what's called passive consent in some other research areas. And that is that you don't actually consent, you just ask people to respond if they don't want to participate in the research. And, of course, it isn't actually consent because you never document that the persons are giving you their agreement ahead of time.

DR. KING: Bear in mind that my discussion pertained to a situation in which a person had given a sample for whose use she had already consented. Right, specifically to that situation. When we begin new studies, they are all opt-in. Right. We are talking about in the tomoxofin case, a situation in which all participants, or virtually all participants, gave a blood sample five to eight years ago-it has to be at least five because four years ago VSRA-1 was cloned-and they said, "Yes, you may use this blood sample for biological markers." But because the word genes was not used, BRCA-1 and 2, this ... all this other concern arose.

So these people have already consented, the materials are stored, so it's, as Alta would say, the second step in a process where original consent was obtained. But the question was how does that consent apply to this second situation.

DR. SCOTT-JONES: Okay, so your statement, "opting in will kill the field" was not meant more generally?

DR. KING: It was meant to apply to the situation in which there are stored materials, which were...which are going to be used anonymously, and which were obtained for reasons which in the context of the historic time made perfectly good sense.

MS. CHARO: I'm now...I just want to make sure I understand your answer. The...let me just run a couple of scenarios by you and ask you which ones you're referring to -this may be the easiest way for me to get it straight. You've got a lot of samples that were originally collected in an explicitly-research context in which people said, yes you may do research on my samples. And the problem is that the research that was envisioned at that time does not encompass today's research, and so you're faced with what should I do to go back for a new stage of research: opt in or opt out or nothing. And I'm assuming that ideally you would like to be able to retain the linkages, get the best scientific work out of this. And here your claim would be that an opt-in strategy would kill this area of research.

DR. KING: Thinking in terms of large cohort studies, yes. Assuming that we want to retain the links, if we are ...

MS. CHARO: Right, right, of course. If you don't retain the links actually you don't need to be doing any of this stuff.

DR. KING: I need to take that on a little sign home with me.

DR. COX: We're going to have it on a plaque.

DR. SHAPIRO: David's been busy tattooing things on people's bodies all day long here.

MS. CHARO: You've got a bunch of samples that were collected-not in a research context, they were collected in a clinical context. They are sitting in all sorts of path labs, and you would like to access these. It will be the first time these people are ever being

contacted about the possibility of being research subjects. You would like to retain the links in order to maintain highest degree of scientific importance for your work. Are you saying that an opt-in strategy cannot be tolerated here either, because of its cost to science?

DR. KING: Those weren't the questions I was addressing because it doesn't happen to be the one I'm up against. But I believe it is true. Let me say it in a slightly different way, and that is that I think that the number of important studies that could be done will be drastically reduced if that scenario is precluded, if everyone whose biopsy or pathology specimen now sits at UCSF must be contacted individually before that specimen with concomitant follow-up data for the future can be used for a study. How, what would I personally do in a real situation? I would have to confront the real situation and decide, because typically we use these anonymously and we don't try to follow up. I've belabored this already. But there will be enormous medical costs if we cannot use follow-up information in those scenarios.

MS. CHARO: And one last thing, because we were talking earlier about economics and practicability, etc., and now, I don't know, many of you may have had the experience I've had recently, I changed phone companies. And that means that I have now seen exactly what money can buy in terms of constant re-contact. And I'm wondering ifXyou now, anybody who's been through this knows what I'm talking about, right? If this were considered a serious concern, if the kind of effort was put into going back to the people whose samples are currently in collections around the country and getting prospective, general, or layered consent that would obviate these problems in the future with appropriate incentive, like the ones that ATT, MCI, and Sprint keep offering me, keep upping the ante on, right, would you think it's money well spent? Or do you think that this is really just not important enough that the risks are not great enough that this is an overly protective stance that we are taking?

DR. KING: It think that would be an enormous waste of money. And I think it would even be more negative than that. I think it would carry out the specter of Big Brother to an extent that you wouldn't have anticipated, that people would have said, how on earth did you find me, what are you doing following me around? You've got my specimen, goodness sakes, why don't you just use it, why are you haunting me, why are

following me? I think we have to recognize that there are downsides to invading people's privacy, and I would consider it, from my case, I had a lot of surgery when I was a little kid, if somebody got back in touch with me and said, we now know where you have been all these years, we have found you and we want to know about this specimen and can we use it, my first reaction would not be, sure you could use my specimen, although that doesn't bother me if they use my specimen. But it would be what are you doing tracking me down? So I mean Big Brother cuts both ways. Big Brother can be paternalistic and it can still be aggravating to be followed by Big Brother. And I'm speaking now not as a geneticist, just as a person who was a kid with a lot of surgery, you know.

DR. SHAPIRO: Okay, well thank you very much. I really appreciate very much your coming here, it's been very fascinating to have this discussion with you; I wish we could spend more time. Unfortunately we have to get on with parts of our agenda. Thank you very much for coming. Thank you. Let me tell you the good news and the bad news. The good news is we're going to take a five-minute break; the bad news is by the time you come back you should have read page 3 and 4 of this memo so we can help Jim get that discussion started, which is really a critical... It's the, excuse me, it's the backbone of the capacity report. But the items on the next two pages will be quite important, and we talked around them for a long time, so if we can come back in five or ten minutes having read, or reread as the case may be, that part would be very helpful. Is that all right, Jim?

DR. CHILDRESS: That's right, and we will pick up where we left off because there are still some comments on page 2 at the bottom. And we'll also have to pick up an earlier one we omitted. I don't know whether Laurie's going to be joining us or not.

HAROLD: Okay, let's get going. There are still one or two Commissioners who will join us in a few moments, but why don't we begin. Let me turn the chair over to Jim to pick up our conversation of late morning.

DR. CHILDRESS: All right, if we could return to the bottom of page 2, and pick up the recommendation number two that we were discussion from pages 161-162, and think about how to formulate what we want to say if we've not been able to do so. And I'll just make one comment again and then I know that Bernie and Alta both want to get in on this. In fact, you had your hands up before we took the break this morning. This is the question that...basicallyXand I had a chance to talk with Jonathan and someone else since the session this morningXit does seem to me that we have two sorts of concerns

here. One concern is, again, that we not exploit a particular group or class as those with mental disorders that affect or may affect decisionmaking capacity, by targeting them in a research protocol that could be done as well with some other group. And that's basically a nonexploitation requirement of a principle of justice. But we also have another concern and that is that individuals who have mental disorders that may affect their decisionmaking capacity not be excluded from protocols that, just because they have those conditions, particularly, for instance, if they could give consent. So...and some of those may be valuable to them as members of the group or individuals with particular conditions. So the critical question is how we state this and whether we want to change what we've written in a way to clarify the points we want to make. Bernie, do you want to get on this now?

DR. LO: I'll pass.

DR. SHAPIRO: My view of this is that if it is a study related to mental disorder from which they are suffering, such as the example of Larry in proposals and text here, then I don't see...there's certainly no reason to exclude them, every reason to include them under appropriate circumstances and so on. That's not an issue, I think, although we discussed it, we all agree with that. Then there's a second question of whether what... what is said here, research that is indirectly related to their mental disorder. I don't know quite what that means, but if it means it has some but not very direct relationship, if that's what it means, then I would come down the same place.

I would favor under appropriate circumstances that they be included. If it bears no relation, or no known relation to their mental disorder, to me it seems that the benefit of having them be able to participate if they consent are outweighed by my other concern, maybe that we not be in a position of taking advantage of this group. If it could be as easily and as well done in other groups, I'm a little worried about that.

DR. CHILDRESS: That's as a group because we think, again, the individual who may want to enter a chemotherapy protocol for cancer, who has a mental disorder that may affect decisionmaking capacity, but who knows that? It seems to me that at that point we're treating them not as a member of a group of those with mental disorders but rather as...is the protocol can be done with, and is being done with the general population, then it seems to me that a person who has a mental disorder that may affect decisionmaking capacity can give consent. That's why I distinguish targeting those with mental disorders as a population or group or protocol, and that I think is ruling out, unless it really is necessary to do with that population, versus a study that is being done with the general

population for which a particular individual with mental disorders that may affect decisionmaking capacity might benefit.

DR. SHAPIRO: I agree. It's hard to distinguish the individual level from the group level.

DR. MORENO: In that spirit, Jim, maybe we should replace the word "involving" with the word "targeting" in the statement that appears on page 162. "An IRB should not approve research targeting, or may not approve research targeting subjects with mental disorders," etc.

DR. CHILDRESS: All right, there were several hands. Trish.

MS. BACKLAR: I'm actually going to repeat what I said when we broke off...what if you have somebody who has a bipolar disease and cancer and is perfectly capable of making a decision about involving herself or himself in a cancer study? Mary Claire's study or whatever?

DR. CHILDRESS: We would also actually permit such a person being involved even without his or her consent. In a therapeutic trial.

MS. CHARO: If I'm understanding correctly, what Jonathan is suggesting is that the language make it clear that what you could not do is target people with bipolar disorder in order to recruit them primarily or specifically into this study. But if one happens to respond to a general recruitment call and is capable of consent, there's no problem.

DR. MORENO: Right, that's the spirit of it anyway, Alta.

DR. CHILDRESS: Is this direction one that we think is workable?

MS. BACKLAR: And of course at the same time we want to make sure that people are not being recruited into a study just because they're mentally ill and they could be easily used in a study which has nothing to do with their illness.

DR. SHAPIRO: That's what the target, I think, is supposed to mean.

DR. CHILDRESS: Right.

DR. COX: No, I really think that to be so paternalistic, because someone falls in this class, to abrogate their options as an individual, is just too much. I mean, it's too

much to handle. So, I think that's one of the points that Laurie was trying to make about this, so we have to really maintain the individual's right to choose. If we take that away in terms of protecting them, then what are we doing?

DR. CHILDRESS: Other points, Bernie?

DR. LO: Yes, I just would like to suggest that the explanation that you gave, Jim, about four minutes ago be incorporated so that it really clarifies things.

DR. CHILDRESS: Okay, other points on this one? All right, if not, let's turn now to...let's actually go back and pick up the first page and the second bullet because it's closely connected to the one at the top of page three, and that is whether we're going to stay with two categories of risk, whether we want to go in the direction of three. So let's deal with that question first, the two categories of risk versus three. And then we'll see how this works out on the top of page three. So, back on page one, two categories of risk...Alta?

MS. CHARO: Jim, especially in light of Mary Claire King's presentation, which gave us what Eric Meslin calls a boundary case, that is a kind of example of exactly what might be lost if the regulations that exist or that are being proposed can't accommodate it, I feel like in this area of two categories of risk where the second category prohibits research to a large degree if consent can't be obtained, with very few exceptions, that it might be very illuminating to find out what would be lost. And although I'm hoping in the public reaction that we're going to get some proposals about what might be lost, it also occurred to me that we might find out a little bit by looking backwards. If we were to have on our staff or by a contractor somebody go to a few of the most prominent journals in these fields for the last 20 years and just take a sample of some of the publications and the studies that are described there, and ask for the methodology of each study, could it be done under the rules that we're proposing, and help us understand which ones couldn't have been done so we'd have a very concrete idea of what would have been lost had the things we're proposing today been adopted 20 years ago. It might help us to understand exactly what the quid pro quo here is for the protection of subjects that up until now has been adopted as the view of the majority of the Commissioners, although not without Laurie Flynn's dissent. I would find that helpful in getting confident in my own judgment.

DR. CHILDRESS: I think that's a very good point, and let's say if others want to

comment on it. Bernie.

DR. LO: I agree, that you've been concerned at the way a lot of research which is maybe not a whole lot more than minimal risk will be for all intents and purposes virtually impossible to carry out. And I guess I would be more forward-looking and go to reputable, thoughtful, sensitive, investigators who care about patients and not harming them, and say what types of pivotal studies would be either precluded or virtually impossible to carry out if Appendix 2 were really implemented?

DR. CHILDRESS: We could provide a summary of our recommendations and the flow chart and actually get feedback. Eric, and then I have some other comments.

DR. MESLIN: Just as a reminder, the purpose of the public comment, period, is twofold. One, the document is out on the Web, was placed there last week, and as a reminder, we sent over a hundred letters with copies of the report, the entire report, to individuals, both of the kind that Bernie has described and individuals reflecting advocacy organizations, patients' organizations, researchers-what we felt was a broad cross-section of the community. And the letter, a copy of which is in your briefing book in advance of this section, which describes what we were asking for, I hope...gets to some of these issues. We did not specifically ask the question that Alta has, I think, quite appropriately raised, what would be lost if the document that you now have in front of you were implemented tomorrow. But we're hoping that by reading through that letter that that kind of message will come through. In the event that it doesn't, we do have the luxury of continuing that process. And the second point is just to remind about the protocol and consent form review which won't go back 20 years. It will only be going back at this point to 1995, and that will give us at least a sense on the permission side as to what research looks like now or has looked like over the last few years. So, not exactly what you're asking for, Bernie, but that solicitation was intended to elicit some of those points.

MS. CHARO: I'm hoping we get all that, and I will value it tremendously. I'm suggesting a retrospective look as well for a very specific reason. My experience, my limited experience, has been that under some circumstances people in the scientific community will promise the moon. When they need money or they offer restrictions they'll talk about all the great things that will happen. And then when somebody worries about the consequences of all this, then they'll say "oh, it's not really going to happen" or

"it's really decades away." I mean that's just a human tendency. And by doing a retrospective, you get away from speculation about what would be lost and what the conditions of research would be in terms of the harms or the fears or the discomforts that would be suffered by the subjects. You can actually look in a more concrete way at actually what precisely would have been lost and what exactly was the experience of those subjects who might have been enrolled without having been able to adequately excuse themselves from the research. So, I'm still kind of interested in doing this if it's not too unwieldy, which it may well be.

DR. MORENO: I think the results of such a sampling would be interesting. However, we know in advance that there is only one set of circumstances in which studies that may have been done would be precluded under these recommendations without Secretarial approval. And that is greater than the minimal risk, no benefit studies, without informed consent. Now that...either that is a very small universe and/or it is universe that most people on the Commission, I gather, would not prefer to see continue anyway.

MS. CHARO: But this is the place where the two categories thing becomes crucial because the question would be, Would some of the things that we would have lost been retained under a rule that had a slight increment over minimal risk third category? In other words, a kind of test of the effect of having a third category.

DR. MORENO: Yes. What concerns me, of course, and I know you've thought about this too, is how we assess what counts as falling into greater than or a little more or a lot more. And that's why I am somewhat concerned that the information that might be available with a lot of effort from such an investigation may be minimal.

DR. LO: You know, again, I think what I most need is a real-life example. I mean it's one thing in the abstract think that we may be missing some important...we may be precluding some important research. And some like Mary Claire King say, let me tell you about a study, let me tell you how we tried our best to make it work, and why we decided to do it in a way that very clearly, I think, compromises extremely valuable knowledge, that's really important. So I can't tell what the size of this box is until I hear some real examples. I think it's very hard to do this abstractly without thinking of some specific studies in mind. And that's why I think we need some help with it.

DR. CHILDRESS: Before I get Diane and Trish, would it be possible to select a

dozen or so of the people to whom have already written and say, look, we've had this particular concern? We know it really doesn't matter, in many ways it's a biased group, because what we're really interested in is can you identify some studies that are really important, that would not be...that could not be done under our framework.

And actually it's important to have those who would be most suspicious of our recommendations look at that. To show us the studies, and if we could find that then that would actually be helpful to us, I think. Would that be a plausible way to proceed? See any reason not to do that?

DR. COX: We need to remember though, that they could not have been done with this kind of subject. Many studies have...the way the brain lights up under various conditions can be done with other subjects.

DR. MIIKE: Can I ask a point of clarification? If we have a third category, what are the additional conditions that we would impose on it compared to the two categories that we have now?

MS. CHARO: It's hard to see what the value is if it increases the number of categories.

DR. SHAPIRO: I agree with that.

MS. CHARO: You might accomplish the same thing just by allowing some of the procedures to be placed in the minimal risk category. I think when you start with ill-defined, fuzzy categories like slight increment over minimal risk, you step out on the slippery slope that might allow you to infinitely increase the categories when you wanted to allow more research to be done with fewer restrictions. If we could categorize procedures or techniques as risky or involving only minimal risk or no risk, I wouldn't see what the category would be.

DR. CHILDRESS: One problem with that is that there already is a set of regulations and tradition of interpretation of minimal risk versus more than greater minimal risk and so we have to be able to tie into those. We can't simply say well, this procedure you want to do, this as minimal risk. It seems to me that that's going to end up with a similar set of problems. Trish?

MS. BACKLAR: As I'm listening to this, I'm worried that we're going to go down the slippery slope of the human genome of the human biological material report. And that we're going to get terribly slowed down. But I think that one of the things that's

extremely difficult here, and in all of these reports, is that when we identify these things we do it in a sense with thick fingers, and the cases themselves are going to explain themselves so the research protocol will give us, or hopefully give the reviewers some better idea of where it will fit.

Also, the aspect of this which is so very difficultXand from the very beginning we've known thatXis that we are identifying a population which is very buried. And what may be minimal risk for some members of this population and not for others will be altered by what their particular disease category may be.

MS. CHARO: I've been an advocate of keeping the two category regime with a highly protective standard for the greater than minimal risk category all along. But I'm still searching for something that'll help me be confident in that judgment. Now, we have a model for a three-tiered system in the area of research with children in which they do use this intermediate category and in which they have a three-tiered protectionist scheme. I wonder if it would be possible to supplement the letters that have been sent already, perhaps, with a smattering of letters to perhaps the chairs of IRBs around the country, at children's hospitals perhaps, as well as at a couple places that don't have a large pediatric population asking them about their experience in applying a three-tiered system for children's research, how hard has it been to be confident in their own judgments about what belongs in what categories. This would be a prelude to, Larry, worrying about what should belong in each of these three categories as far as protective measures should we decide to backtrack and move toward a three-tiered system. But one of the objections to a three-tiered system has been that it can be unwieldy, complicated, difficult to enforce, etc. And maybe some feedback on the one example we have out there would be helpful.

DR. LO: I think this discussion needs to tie in with the discussion of what's in the boxes on the bottom level. So one of my concerns is not so much with the yes/no dichotomy as to what the implications of being in the no column now as I read down the page. Again, I think in our draft I don't think we give a convincing explanation of why we chose what is contained in these two boxes. So although it certainly makes sense to be more stringent for the no rather than the yes in terms of unable to give informed consent under the no direct benefit, greater than minimal risk, why are we going to prohibit it without Secretarial approval and not some other set of protections that are less stringent than that? So part of it is sort of what the implications are being in the sort of most restrictive set of shoeboxes.

DR. CHILDRESS: And I think that really is not spelled out clearly in the text. I think the Secretary aside, wouldn't you agree, Jonathan, that something we would need if we're going to keep that- to really work up further, and that obviously is the connecting question on page 3, that's connected to the one we're just dealing with. Let's see if there's anything else you want to say about the proposal out on the table about how we might get some additional information out. Eric, then Jonathan, then there was a hand here.

DR. MESLIN: I was just going to make a proposal on behalf of staff, if that would be helpful, which uses Alta's suggestion. We can both contact directly individuals to whom we have already sent letters and ask them to provide us with some specific examples. I think phone conversations might be a helpful way of emphasizing our interest. We have, as I say, 114 folks. I can assure the Commission that probably 15 or 20 at the very least would be delighted to provide us with some specific case examples of the kind that Alta is describing, plus or minus the IRB Chair idea. I think the idea of the two or three categories in IRB Chairs being asked for their experience can also be done through either a telephone solicitation or a letter solicitation. Jonathan was going to interrupt me, sorry.

DR. MORENO: Sorry. But I think the critical question surely is not how hard or easy has it been for IRBs to use the three boxes for kids. The critical question is how appropriate have those choices been. And I have some doubts, speaking professionally, about how appropriate some of those choices have been. This methodology will not get to that. The only way to do that is to convene a subcommittee, a super-IRB, to look retrospectively and reevaluate some of those judgments. I think to get a meaty result from this aspect of what you're suggesting is going to be harder than just asking IRB Chairs to respond in a simple fashion.

DR. SCOTT-JONES: I would just like to again try to make a case for the two categories over the three. I think that when you put any study into categories, whether two or three, you could always possibly make a ranking of those experiments or studies within the category and claim that some are more risky than others. So you will never create a situation where when you use the categories you have a homogenous grouping of studies within the categories. So I think it's futile to try and create another category so that you're always putting in those categories studies that are at the same level of risk. That just isn't the way studies will be. Studies will be very diverse, they'll be very different. So I think there's futility in this effort to resolve a problem by creating categories. I think

the way you resolve it is really by having the investigators and IRBs, anyone who's in a position to comment on the work, be very careful in how you go about assessing risk because that's something that's very difficult to do. And I think that's where the energy needs to be placed, not in the number of categories that one uses. Three categories isn't superior to two when you have a very difficult decision and you're still going to have a lot of variability that's more than three points.

DR. CHILDRESS: Before we get Harold in, let me just...as I understand sort of the direction we've gone from Alta, and I hope I don't misinterpret you here, it's something I share hearing the previous conversation, namely, not that we're calling into question the two categories. What we want to do is get the best information we can to test those categories before our final report. We heard some things in the previous discussion that at least might cast light on some of the issues and the genetics of stored tissues, now we'll report a little different way. What we'd like to know are there some cases like that that would pose problems for us here. So it's not so much that we're challenging the two tier but really sort of testing it to see if we have actually been able to want to. Is that the direction you were going, Alta? I just wanted to share that.

MS. CHARO: Absolutely. Jonathan has impressed me with how difficult a task it will be, and I simply commend the staff with the task of seeing if it's possible.

DR. CHILDRESS: It's possible.

MS. CHARO: It may not be, but if it's possible to get anything useful.

DR. SHAPIRO: Can I make a comment about this? This is not...I don't think we should think about this as whether we like two or three or even asking the question which couldn't go ahead with two or three, which incidentally is impossible to answer, unless you know what level of protections are you going to put within each category. Now if we distinguish three, but two of them have the same level of protections, it's totally irrelevant to the question. So...the question we've been talking about, then, is not well-defined.

And so I think if I could suggest that if we go ahead of it and then see what protections come along the bottom line here. Then ask ourselves the question, if something were a minimal increase over, excuse me, whatever the terminology, a small increase over minimal risk, would the protections vary at all? If the answer is no, then the whole study's not necessary. And so if we get to that point, maybe we again can circle back here and see if we have a well-defined question to ask. And as I look at it, if you look at the diagram,

which is the simplest thing to look at to get a quick look, what Bernie's been referring to, it's on 173, and ask yourself all right, if there were a small increase over minimal risk, would it need any boxes here or just leave the same old boxes. That's exactly what we found out, incidentally, when we got bogged down in the biological materials. We had all these different boxes and they all mounted to the same thing.

MS. CHARO: But the answer here is actually that there would be a difference, and this is what Laurie has been so upset about, that if we had...

DR. SHAPIRO: Only if we say there will be a difference. We have to decide that.

MS. CHARO: Now we're moving into the land of totality, of course, but this is the essence of her objections. She would like to have possibility of some kind of surrogate consent process or nontherapeutic studies that are only a minor increment over minimal risk. And that would be the new category. A full panoply of all the protections, all the other stuff mightX

DR. SHAPIRO: That's right, it would be if you looked down at our diagram or something, it's that it could get into the box that's second from the left.

MS. CHARO: Essentially nontherapeutic, minor increment over minimal risk would be treated the way we now treat therapeutic greater than minimal risk. It would move this small group of nontherapeutic studies into a regime of protectiveness akin to what we now use for therapeutic but risky studies. And that's what she would like to have done, and that's where this fight has been focused. I think.

MS. BACKLAR: I think it's helpful to get out of the boxes for a minute and to go back to the reasoning that we originally were talking about-why we saw it as minimal risk or not minimal risk. And that was because we looked at many members of this population, even in minimal risk studies. I just have to use as an example my own studies in which it's clearly minimal risk in which there are certain things that can obtain that I would, even in this study, be concerned about if I had someone in the study and I did not have an outside provider for them in case something went wrong. Not even during the interviews, but for instance because the person was upset about something that occurred in the interview. Now we've already agreed, you don't need to have all these things in place for minimal risk. Right? And so knowing that even in studies which were minimal risk, there is risk for many people in this population. I don't know what

differences you would make with a third group. Am I making sense?

MS. CHARO: All my understanding of Laurie was that she would want the same protections for therapeutic but risky research to apply to nontherapeutic, only a minor increase over minimal risk research. So that would give you the answer of what those protective measures would be.

DR. LO: Let me try to take a different tack, which is to offer an example of the study that I'm concerned about landing in the "prohibited without special Secretarial approval" category. So I'm going to try and develop a scenario for a study which is more than minimal risk, of no therapeutic, no potential direct benefit to subjects, and the subjects are unlikely to be capable of giving informed consent. Okay, and that's a study where you pick your disorderXsevere schizophrenia, severe bipolar diseaseXand the aim of the study is to try and correlate, just to test an association between results on imaging studies and levels of neurotransmitters in the brain. And the goal of the study is to try and find surrogate endpoints for screening candidate new therapies so that you can more effectively screen out candidate new drugs. And I think it fits with the notion that there's going to be a lot clearer design of drugs and a lot more candidate drugs and they want to test them more efficiently, to throw out the ones that aren't going to be of benefit. So the goal would be to try to develop surrogate markers by using imaging studies where you could identify drugs and new therapies that might be potentially beneficial.

So I'm trying to construct a case that although it's not directly beneficial, it provides basic knowledge of the pathophysiology of the person's condition, which could then lead to therapy. So I'm trying to understand the concepts that underlie some of the boxes in the children's research thing. We've already said that certainly a lot of our puncture and also MRI studies are more than minimal risk for this population. And I guess I would like to argue that to make those studies acceptable only with special Secretarial approval basically means you're not going to do the studies, realistically. And I'd like to say is there something short of that that involves surrogate consent, prior research office directions when they're in remission, no apparent dissent, health care advisor.... But is there any sentiment that, for those clients who have started, are people willing to have some other box that's filled with something other than just "prohibited without special Secretarial approval"? And I don't know if that's the stone answer I'd like to get. You know people are in the field to help construct a scenario but it seems to me that there may well be studies where we'd want to have more protection than is now available but something not

quite as stringent as Secretarial approval.

DR. CHILDRESS: Just pick up on part of that before we get others in...if you could, for instance, get the advanced planning as sort of discussed here which your example seemed to suggest, and that would actually pull it over in the category of "yes" in terms of capable of giving consent. That is, if a person would have a period where a person could engage in advance planning, that is actually included as a possibility.

DR. LO: But you're saying it would be under the left column.

DR. MORENO: Yes, it would fit. So that would be taken care of, but there may be other, even beyond that, there may be other situations where you might be proposing other kinds of ....

DR. LO: Jim, but this was not direct benefit to subject.

DR. CHILDRESS: That's right. So that would be included.

DR. MORENO: If they could do advance planning, the other alternative that I've heard some people talk about advocating is using less affected subjects in the beginning, try to develop strategies that are more likely to be beneficial, and again in that box the subsequent studies.

DR. LO: But the box doesn't reflect that though.

DR. CHILDRESS: ...it includes it. If you look at 154 for example, page 154, it's included. But the box doesn't clearly capture that. That's one of the shortcomings of the box, but it's in the text.

DR. MESLIN: It's 154, lines 3 to 5 in the text, which I don't think are captured in the boxes of 173. And the sentence reads, "As is the case for studies that present a potential direct benefit", and this is still under the category of no direct benefit, "their consent to a particular study may be obtained in advance of a period of incapacity." That line which I just read on 154 is included under the section, "greater than minimal risk for research that is not potentially beneficial to subjects." And the appendix does not actually have a box. An error in the appendix we've got, an omission, I'm sorry.

MS. BACKLAR: And there is something here that I'm concerned about in this box that we have where it doesn't offer potential benefit, the box that Bernie has been looking at. And you get down, "Are subjects likely to be capable of giving informed consent." Now I've lost the box where we were looking...that's the box...so if they're likely

to be able to give informed consent, well then there is much less problem, right? And so what is the ... I'm not quite certain what you're concerned about.

DR. LO: Well, it's the difference between giving informed consent at the time you're actually going to do the procedure, and giving the informed consent in remission when you're eligible for the study because that's not what the study's about.

DR. CHILDRESS: And so what we're saying is the box doesn't match the text, and the text does include possibility of advanced planning.

MS. BACKLAR: But that is then what concerns me. I want to make sure that that advance planning is always for a particular study.

DR. MORENO: The text also does say that.

MS. BACKLAR: I don't want to see that kind of blanket. I'm saying it's okay to anything.

DR. MORENO: It's not a blank check, it's a particular study.

MS. BACKLAR: Okay, that's what I ... just wanted to verify that.

DR. MORENO: The text shows that.

DR. CHILDRESS: Other points on this? There's...Bernie, do you, excuse me, there may be other aspects you're concerned about as well.

DR. LO: Again, there are different types of advance directives, and some are more to specific than others. If we're saying you may only give an advance directive to one specific protocol, we're going to run into the same troubles that Mary Claire King told us about with, say dementia, where you give one crack you're giving your consent, two years later there's something else which is very comparable to what you've consented for but you're saying but no, you didn't specifically consent to that so we can't do it. So I'm a little...I mean I don't want a blanket consent to anything. But it seems to me that if I want to consent when I'm demented to imaging studies that, as best as people can tell, create the risk of anxiety and minor irritation from getting an IV put in, if there's a new type of imaging study that isn't a PET scan and I didn't consent to it, I'm a little concerned of someone saying well, you didn't consent to this specific thing so you can't do it. Where capacity is fluctuating, you can always go back. But you know, all the research on Alzheimer's you can't do.

DR. SCOTT-JONES: Could I just ask a question following up on what Bernie's

saying? Bernie, I guess it's not clear to me, why would you want the person to be in one study and then another and then another?

DR. LO: No, no, I'm not saying one study, then another, then another. But I'm saying...it's a different issue, but if I'm saying prospective consent and by the time I'm eligible for the study, it's a different protocol, it's a different generation scanner, different type of scan, or something. I mean how precise do I have to be in a degenerative condition. I'm not saying use me for every single study that comes along. And you can say you only get to be in one of these studies.

DR. MIIKE: I don't think that's our notion on what consent is. I thought that we're talking about consent very close to the onset of a particular study. So you're talking more like an advance directive like....

DR. LO: Yes, I'd be interested in it but they're spreading the research apart. I don't think we've ever considered that as a consent, right?

DR. SHAPIRO: Bernie, is it tough at all to observe, maybe there's just diversion for which I apologize, that if two new generations' ideas and procedures come along, as was presented to you this afternoon. And in lots of cases, unfortunately new generations of potential subjects come along. And therefore you don't ... now there was a very special case here because they want to follow pedigrees over a long period of time and that was a very special, important case. I don't know, I just ask that question now, I don't know whether there are analogous cases for these kinds of procedures or not. I just don't know enough about the ideology of the diseases and so on.

DR. MORENO: Some of you have heard my take on this issue before. In general, my view is that our society has not endorsed a notion of anybody being able to give blanket endorsement to research participation in advance-for any population. I don't know why we would want to start with a population that has instrumental disorders. I need help from the lawyers here, but I don't know any state legislation that creates a legal device that would enable me as a relatively competent person, still in spite of my work for NBAC, to authorize my use in a blanket sense 70 years from now, 50 years from now in research.

DR. LO: I guess it seems to me there's a big difference between blanket consent and consent for a more well-defined study. I mean it's the problem with advance directives. I mean if you're going to restrict it only to guessing the specific interventions of specific study, it's going to be very, very narrow.

DR. MORENO: But again in the case of traditional advance directives, at least, as a notion of therapeutic benefit, we lack that here. What we're really talking about here is giving one's body to science, while one is still alive. And that's not...my understanding is that so far we haven't discussed that question.

DR. LO: Well, I think that if, again to use the analogy from children's choices, if pathophysiology of that condition is important to study as the basis for future benefit, there is some value to wanting to do it. And also it seems to me there are different types of risks. So I think blanket consent means you can do anything. I'm saying that drawing on this notion of a little more than minimal risk seems to me there are some things that are risky but we're not talking about the kinds of side effects you get with chemotherapy or major surgery. You're talking about things which are transient, which people may not necessarily remember which are not...don't lead to further problems.

I think to put everything together and say you can't do that without Secretarial approval, I think we may be giving up a lot and I think I'll just wait and see what people in the field have to say.

DR. MIIKE: But if they can give consent it doesn't fall in that category. It's only when they're incapable of giving consent.

DR. LO: Right, right, and I'm saying that if they gave consent before but not to that exact study but something awfully, awfully close, and it's just pathophysiology, and not a whole lot more than minimal risk, are we going to say can't do it without Secretarial approval?

MS. BACKLAR: I would be terribly afraid that somebody who is eagerly doing research in an area that you would say is not so different that this would bend in ways that you might end up having people in research protocols which were far away from what they would precisely have agreed to be in. And then I think about Al Jonsen yesterday talking about how their view was shaped by Hans Jonas's view that they weren't going to have this utilitarian consequence on list balancing. And I'm concerned about the same thing here. I want to make sure that we have adequate protections for people who may not be able to protect themselves.

DR. CHILDRESS: Are there other points that should be made now, particularly about the section on page 3 and then the materials that follow? Under the heading of "Research Involving Greater than Minimal Risk that does not offer the prospect of direct benefit to subjects." We've already touched on a fair amount of this, moving from the two

categories of risk. But are there other things we need to say about this? Again, one thing we don't have in the text is a very clear explanation of the approval by the secretary. We do discuss it on page 152, I think it's some place in the text that I found it. But are there other points that you want to make about this, and then about ways to harmonize what we say in the text? Again, I think most of those can be handled in an editorial way. But Harold had recommended that people look over pages 3 and 4 particularly carefully for these related points.

DR. MIIKE: You know the top of page 3 is also related to the last point on page 4.

DR. CHILDRESS: These all four go together here. Pages 3 and 4 work together involving the point at the top, plus then how you'd work out the understanding of individuals who can consent and those who cannot, and then the last part that you know. So what do you want to say about these two pages?

DR. MIIKE: Can I comment on the last part of page 4? It seems to ... it doesn't make sense because it says, "for individuals who cannot consent," you're going to require before they even go to Secretarial approval that they would have given their consent in advance. Well but you said...you're recommending that they be changed to include both conditions. Aren't you doing that?

DR. MESLIN: They would not be jointly necessary but one could occur or not. That's a confusion in the text which we would like to clarify. But there are two places where individuals who cannot now consent could participate.

MS. CHARO: You want to be consistently A or B.

DR. MIIKE: Okay, I was reading that recommendation and I thought that you were adding the A to B.

MS. BACKLAR: We are now looking at for individuals. We skipped over this middle section that I thought we were looking at and we're looking at this now on page 4, the bottom of page 4 for individuals who cannot consent? Is that correct?

DR. CHILDRESS: That's right, it ties back to the top of page 3. Okay, we've...basically is right...we've been skipping...the middle part..it's organized in a confusing way. But this part on individuals who can consent, on the middle of page 3 to the top of page 4 really is a matter to be handled editorially. What we're really talking

about is this first paragraph on the top of page 3 and the part that Larry directed us for at the bottom of page 4, right? Those are the two connected passages and basically what we want to say about the requirement of consent for participation and research involving greater than minimal risk, that it does not offer the prospective direct benefit. And what we want to say about Secretarial approval.

DR. LO: Right. Now, Larry's question, then, I thought somebody said this box down here should read either Secretarial approval, is it an prior consent in advance of the...

MS. CHARO: Or.

DR. MIIKE: No, that box is okay, Bernie, because the left side of the box would say that there was consent obtained. So it mirrors the box, it's either/or. Neither consent was obtained or consent was not obtained, Secretarial approval was.

MS. BACKLAR: Okay, okay, all right. This is not as confusing as we have made it.

MS. CHARO: All the people here who are fuzzy after meeting too long raise their hands.

DR. CHILDRESS: We're reaching the end of the day. Yes, any other points that need to be made about this. And obviously we will have to continue some of the discussion.

MS. BACKLAR: I think I need a surrogate to make some decisions for me.

DR. CHILDRESS: And need to listen very carefully to Laurie's arguments, it may well be we'll end up obviously with individuals filing dissents to different parts of the part after we've gone through. Are there other points that need to be made about 3, pages 3 and 4? I have just a couple other points I'd like to raise, and I'm sure other Commissioners do to about the draft and then ... other points about 3 and 4? Let me offer just a few observations. Again, I think we've made real progress on this draft, and thanks to all those who've been involved in it. One thing that I think may not have adequately reflected in our recommendations and in our special protections is something that came up, comes up in the report earlier, and something we've talked about before. And that has to do with the contextual elements that the IRB might consider. We don't bring in, for instance, consideration of institutionalized versus noninstitutionalized. Some of these contextual factors I don't think we really worked in very well even to our guidance to IRBs, and that's one thing we might try to do. Then a few other points I have

may appear to be editorial in nature but I think they're not. I think they're actually more conceptual than they are editorial, and I'd like to make them and get them out on the table because they affect the way we think about the structure of the report.

If you look at the table of contents, I feel very strongly that we ought to reverse the order of Chapter 4 and 5. Because we have Chapter 3, and I'm going to argue for retitling that, that really focuses on voluntary informed choice. And we have Chapter 5 that deals with advanced planning, surrogate decisionmaking, and the like. And we have in between those two a chapter on risk and benefit. And it seems to me that five really follows from three and that's a structural matter we ought to take care of. So it's more than editorial, it really is conceptual matter, how you can see the project. I think that connected with that that we really need to retitle Chapters 3 and 5, because we've got a criticism of the draft that focused on the fact that we don't really deal with informed consent, but actually Chapter 3 is on informed consent and the limitations of informed consent. But that's not really reflected in the title, so we need something likeXand I'm just throw these out, these are hardly well-thought throughXbut something like "Informed Consent and Limitations on Decisionmaking Capacity." Because that, first of all, what it means is you've got voluntary informed consent, and then looking at the limitations because of decisional impairment and the like. Or in Chapter 5, which I would suggest would be now Chapter 4, we need something like "Assent, Dissent, Advance Planning and Surrogate Decisionmaking" because even though you can't tell from the table of contents we have here, the whole first part of that is on assent and dissent. And that's where we bring their argument and discussion in the text about how we relate to the National Commission. I think those are...I'd like to propose those unless there are strong objections that could be taken account of when we make the next revision. Those are some of the thoughts I had, what other points would you like to raise about the draft, the recommendations, the framework of protections?

DR. LO: I'd like to readdress the issue of IRBs. As I read through the report, it seems that one of the crucial things we're doing is asking the IRBs to play a more active role in protecting persons with possible impairments in decisionmaking capacity. We really are asking them to do a lot of different things. To put them all in one place, special scrutiny to protocols that intentionally cause harm, identifying problematic study designs, scrutinizing the procedures for evaluating decisionmaking capacity, evaluating the scientific merit of the proposal, determining which supplemental protections are warranted in particular cases.

That's a lot of responsibility. And I think I want to put that in the context of a lot of growing concern now that IRBs simply don't have the resources, and may not have the expertise to do this. And even taking into account the recommendations to add additional members and to perhaps the audit, which I'm not sure of, I think I have concerns about making so many of our recommendations hinge on a process, a technique, that is of questionable effectiveness doing what it is now supposed to do for a whole host of reasons. And I know we're planning to do a separate report that addresses that, but it seems to me that as part of this report, we need to try and address some of the fissures because frankly an IRB is not going to be able to handle this. I mean they're stretched to the limit. And unless they get a lot of extra funding to do this, I think we're not...the protections we're hoping for are not going to materialize without a very robust, active, IRB at major institutions. So I'm concerned about making the implication realisticXwork in the real world. And there're going to be real costs, we talked earlier this day about monetary costs. I mean we're really talking about asking institutions to make a substantial commitment to our views. That's just not there now.

DR. SCOTT-JONES: Bernie, I see your point about IRBs and the fact that they're overburdened, but what would be your alternative for recommendations that we could make in this report? If we don't make the IRB central in this process, what could we do instead that would be helpful?

DR. LO: Well, I'm not sure I would quite answer it that way. I would say what do we need to say in our report to make the IRBs really capable of taking all these additional tasks. And to really explicitly spell out we understand that IRBs are being asked to do increasing amounts of work; they're dependent on volunteers; don't have enough administrative support. These are things, they may not be trained to think about some of these issues. These are the things that we suggest need to be implemented to make this really feasible.

DR. SHAPIRO: I actually have a lot of sympathy for that. I think that we should find a place in the report to acknowledge the increased burden, the increased set of requirements, and acknowledge the fact that the system as a whole has to find institutions and better support the IRBs themselves. I thought a lot about whether there is an alternative arrangement.

It's not easy to think that with an alternative arrangement that would be anywhere near as

effective. And despite all the limitations, and genuine ones that you have pointed to, I think if we can say something now about the need in this context, at least, to strengthen these institutions in various ways, that would be very helpful and then when we follow that up next year with a report that has more to say about this. So I'm sympathetic to acknowledging this and not pretending that this could be just put on their plate without any ...they'll just do it. I think there's enormous variability in institutions regarding how our IRBs work, how much institutional support they get, how well organized they are and so on. But nevertheless, your point is well taken, I'm sympathetic.

MS. BACKLAR: And there's a section in the report where that could fit in very well because you've started a section, the reason there are extra costs and why one will have to pay for this.

DR. MORENO: I had the opportunity about two months ago to present the draft recommendations to an FDA-OPRR workshop in Albuquerque. And I said at the beginning of the talk that I was afraid they wouldn't like me very much when I got to the end. These were, of course, all IRB people. And I was surprised at the benign response. Now that might be because a lot of these IRBs work with people from Native American communities who already have a high monitoring and reconsenting and so forth in place. Another case, an individual from a very large, research nurse, from a very large academic medical center, said they had already a liaison as I mentioned before who does much of what I've been talking about. And she wasn't put off at all. So this leads me to a practical suggestion. Perhaps what NBAC might want to consider is after this report comes out, is sponsoring a conference, perhaps with another organization, perhaps OPRR, where individuals from some of these institutions could model their work, could model the arrangements that they have already, and give a very practical indication of what kind of institutional vestment it has met. Because I think although many of the larger IRBs, we also knew from the Belmont Report, that about 10 percent of IRBs do 48 percent of the protocols. So there's a small number, they are very stressed. There could be a specifically identified effort to help them make the arrangements they need to make with an assessment of how much it would cost them.

MS. CHARO: First I second the suggestion about a conference; I think it's actually a very nice way of disseminating. I'd like to perhaps even encourage us to take one step beyond what Bernie and Harold have suggested on this text. In the Executive Summary and in the Introduction to the recommendations and whatever short version comes out as well as in the main text, I'd love to see us emphasize that after much

deliberation it was only a nuanced, scaled, complex approach to a range of protections that emerged as a realistic way of managing this problem. But no other solution really seemed to present itself, and that we were perforce required to send this kind of work somewhere, and that the current system either has to be massively changed or massively improved in order to accommodate this work. And to do the same thing in the biological materials report, and to also note in both of them that the structure of human subjects protection in the federal government makes it difficult to make these changes in a regulatory fashion because of not only the decentralized IRB system, but the decentralized authority over human subjects protection in the U.S. government. And in this way truly use these reports to build a record towards next year's report on the human subjects system. Use these very deliberately to introduce some of the difficulties as inevitable unless there is change. Because we already know the system needs to be changed, it's already been stressed beyond its capacities and it's not been enough. So maybe the addition of these, which are our conclusions of what you absolutely have to have to do it right and yet is now a straw on the camel's back will be enough to perhaps get some attention to the need to change the system.

DR. LO: I'd also like to urge us to list out some of the directions we think things need to go. And we have some of this within the report. I mean, inclusion of a meaningful number of persons who have some knowledge of their condition and how to fix potential subjects, increase in staff, particularly for like things like consent monitoring. I'd like to say, you know, for IRBs that routinely see a fair number of protocols that deal with population, there should be some mandatory training for at least some of the people in the IRB to familiarize themselves with what's in this report, and it's not just reading the report.

MS. CHARO: I suspect that when we get the public comments back that a lot of them are going to have a kind of bifurcated look. Nifty ideas, wonderful thoughts, some of them will hate us, you know, but nifty ideas, wonderful thoughts, can't possibly be done because we need X, Y, and Z, and that we should be quoting from those letters, right. Remarks from the field about exactly what makes it...what is necessary to make this possible, I think that would be the most persuasive evidence we could provide. And

they'll give it to us.

DR. LO: Great. But I think ... what am I trying to say here...I guess, to present a solution that we know has a lot of practical difficulties without also taking the lead and suggesting how to overcome difficulties, sort of undermines our report. I think if we just say these are the things that we recommend, yes a lot of this is more for the IRBs, yes, we know it's tough, and please address the situation. That's not going to be as powerful a report as ...and these are some of the things that we recommend that institutions and the federal government do, and this is something simple like allowing extra indirect costs for NIH grants to cover some of this would be a tremendous boon to big research institutions. And I think unless we make some recommendations that really are going to make this happen, it's going to make us look naive.

MS. CHARO: You're not suggesting, though, that we try to actually debate out to the point of consensus specific recommendations on the change of the entire standards we want them to enforce. That they are integrated and you can't separate them. And we all said intellectually that makes perfectly good sense. But as a practical matter we can't manage to figure out how to write a report that covers everything because it's a 10,000-page report that will take 15 years and we will have gone out of existence before we get there. So we were stuck with this practical problem of how to tackle jungles. And I'm wondering if we can avoid the need to try to debate out specific recommendations. If it's enough to say we've gotten evidence from the people who commented that these are the kinds of things that we're bound to wind up recommending eventually, which is better staffing, better financial support, increased representation on the membership of the IRBs, perhaps some possibilities about performance standards or certifications or licensing or some other kind of quality assurance in this system, but we have not yet gotten to that point but we promise you we will by the turn of the century.

DR. MIIKE: My suggestion, Bernie, is that we can all write individual comments on these reports, so if you feel strongly about reemphasizing that point, it's something you can write. But I agree with Alta. We're recommending policy, not operational changes. I don't think we can do both in reports of this.

DR. CHILDRESS: Other points you'd like to make about the draft to guide staff as we try to again go through the several steps we need to produce another version for September?

MS. BACKLAR: I want to make sure that we understand, I want to go back to the

legally authorized representative, and I'm not certain if that's still a little confused. Where we are clear, where it is the person who's the subject who picks that, appoints, chooses a person they trust, and it seemed to me, I found places where it was slipped in...it was imposed upon them, and I'm a little concerned about that confusion.

DR. CHILDRESS: We have both. But the prior would be the individual selection and then in the absence of that the legally authorized representative according to state laws. I think we have both in the report. But there is a priority, there is a ranking.

MS. BACKLAR: Right, I want to make sure that we're very clear about when which happens because one wants the person choosing in every instance where one can have it. And as we know from Greg Sachs' research, people even in certain stages of dementia can still choose people that they trust.

DR. CHILDRESS: Jonathan, any comment?

DR. MORENO: I think it's mainly an editorial matter at this point, Trish. I really think we're pretty clear about that.

MS. BACKLAR: I have marked pages where I find it confusing and we could e-mail about that.

DR. CHILDRESS: Other points? Mr. Chair, it looks as though we're talked out on this subject. Well thank you everyone.

DR. SHAPIRO: Okay, just looking over these issues, I think we've gotten some very good suggestions today which will certainly help us improve this. I think the issue of increment over minimal risk is not going to go away, we're going to have to resolve that. We'll have to see how we can work with it but that's going to be a decision that's still in front of us. I don't see that we came to a conclusion on that today. We didn't force ourselves to vote on just what it is, but I think that's something we ought to pay very careful attention to, and each of us try to think through whether this is really a distinction worth making. And in my view it's because different, as Bernie has suggested, different protections would flow in, i.e., not have to go to the Secretary under certain circumstances or not. And it's really that question we should ask ourselves and see where we all stand on that. And let's try to exchange ideas on that over the next weeks by e-mail and so on so I don't think it's sufficient to leave it to September. We have to sort of...we'll

formulate some ideas and then we have to start working with each other on it.

DR. MESLIN: If I could just make a request couched as a plea, if you have marked-up copies of either of the reports, please give them to any one of the staff members or put them in an envelope and send them back to us. We are engaging an editor so all of the comments of either an editorial nature or conceptual nature will be incorporated into the next draft. Where there are issues of disagreement, I would certainly propose that we use our NBAC e-mail list and that if not just a one-to-one exchange that you share it with everyone on the list, everyone can see what your views are; if you would like to join in the conversation I think that would be most productive to staff. And the sooner, obviously, the better. And we will inform you on an ongoing basis as we receive public comments, not every single one, but as we develop a small critical mass we will share any of those with you in whole or in part. Please feel free to ask, but you will be getting notification of it anyway. We'll also be letting you know about the two consultation activities, the protocol review activity that Trish and Alex and Jim have agreed to assist with. And the other activity is relating to conversations with the Maryland Attorney General's office, the New York Department of Health, and officials at NIH and NIMH as we all begin to review each of the drafts in progress to see where overlap is and gaps may exist.

So we'll keep you as up-to-date, and obviously please communicate with us as regularly as you can.

DR. SHAPIRO: Okay, other comments on this? Because if not, what I ... depending on the will of the Committee, I would suggest a short break and then we go back and see if we can pick up some of the material from the materials report, so to speak, because we hadn't gone through that whole memo and there may be other issues as well. And we have some time here this afternoon, I think we should try to get a little further. Why don't we...it's now about seven or eight minutes after three, why don't we try to be back at 3:20.

DR. SHAPIRO: Colleagues. This morning we were looking over the various recommendations/guidances etc., various statements if you wanted to get some discussion on. We got all the way on page 7 of the memo that came along with the human materials draft. We got through recommendation 6; that is, we got some comments/materials on that and we'll recast that and write along the lines that have been suggested this morning. We now have the two next recommendations, recommendations 7 and 8. Really we perhaps ought to consider together whether one is sort of a notion

again which we may want to change or shift the focus on which recommends that somebody else do something, namely some scientific community, whatever that is, to agree on a set of practices that would eliminate the need for a complex recontact efforts. And recommendation 8, either the therapeutic or the research, clinical or research contents. And recommendation 8 really deals with a similar matter but that has to do with collection of prospective collection of future samples. Now the, as I see it at least, the key issue here is whether and to what extent we want to encourage comment on, say, something in detail about the nature of the consent that would be obtained when collecting materials in ways that would make things simpler in the future. Obviously this deals with prospective samples, and so the question I want to ask is is this something we want to address and if so in what way do we want to address it? Do we think it's a good idea; in that case how do we want to opine on this?

DR. LO: Yes. I mean to pick up on the theme that we were discussing two breaks ago, I think that as with all our recommendations or guidelines, the more we can flesh it out the better.

And for recommendation 7, I think we've already discussed a lot of elements that would need to go into a set of standard practices or best practices, I'm not sure which, and some of them I think include having a community advisory board, having set policies establishing some sort of written procedures for determining both the scientific validity of requests to use the archives and stuff, some mechanism for coding that meets certain standards. And so I think to the extent that we can at least start to point people in the direction and leave it to others to flesh it out, given that practice is evolving and people in the field who are really working on it probably can come up with better ideas in detail than we can, yet still to give some direction I think would be useful.

DR. SHAPIRO: And we do have at least a modest collection of what looked like best practices from our...we got that together and we've got those forms etc. and guidelines, various institutions which I think do a good job here or at least some of the better jobs I've seen. And we can certainly take guidance from that.

DR. LO: And then the other thing which was suggested just a couple of meetings ago was to really give NIH the sort of recommendation that they put some effort into having consensus conferences, training, model training programs, funding people to do research on how to do this better. I mean make it really come alive, put this in as part of

center grants and stuff to facilitate further developments in the field.

MS. CHARO: I think in fact we may, depending on how much time we have and how much attention people want to give it, we may be able to use some of those models that we now have and ourselves pull out the elements that seem to be most essential that we would want to make sure are included in whatever becomes a standard model. Especially keeping in mind Allen Buchanan's analysis of this situation as one in which it's not genuinely informed consent that we're obtaining because it's not really possible to consent to that which you do not know. It's really about prior notification, in which case you want to alert people as much as possible to the variety of things that may happen so that it's a no-surprises scene. And some of the elements that might be pulled out could include such things as the distinction between research that plans to come back to you with its results and research that does not plan to but might yet do it because of something surprising, versus research in which it will never go back to you under any circumstances, no matter how useful it might have been; alerting people to the complexity of state law with regard to discrimination and the fact that in a transient society no matter what your current state laws are you may not know where you'll find yourself on the day when this information might possibly be used. And looking through these forms ourselves and maybe pulling these elements out might give this guidance even more robustness.

DR. COX: I certainly agree with what's been said so far. The ... one point, though, at least in terms of the wording of this. If it could be read that saying the only reason one has these complex recontact schemes is because people are just not being clever enough to avoid them. And there are certain types of research that it's incumbent upon the research to have recontact. So that just so we're sure that the wording isn't done in a way. And there are many types where it doesn't have to be done at all. So just so we're sure that the wording is such that we cover that and have the whole system be as simple as possible because otherwise the implication is that the only reason to ever do this recontacting is because one's just not being thoughtful. And I think that my second point is this one about prior notification. I think it falls under this contact of respect for individuals, so you tell them that these are the possibilities that are about to happen and then as we keep hearing, if it's nine percent of people that say yes, you told me, don't bother me anymore, just go ahead and use it, then that's important information. But it still doesn't obviate the need for the respect of telling people ahead of time by my view. But it's pretty cheap to tell them ahead of time; you don't have to go back and send them a million-dollar questionnaire to ask if it's okay later on.

DR. SHAPIRO: Any other comments? I think with this, as with others, some of the other recommendations and so on we dealt with today does need to be fleshed out in ways that Bernie and others have suggested. And I certainly intend to do so. I just wanted to be sure this was something you thought was important for us to address. Any other comments? On this? Well, what about recommendation 9? At the bottom of page 7. Eric, do you have anything with respect to 9?

DR. MESLIN: This is an issue I think that Bernie has already alluded to with respect to additional feasibility of doing any of these things. So as a guidance it's one thing to offer the idea about the termination for need to reconsent, etc. is important, but that's...that may be more of a judgment or a guidance or educational issue rather than a particular type of recommendation. So I'd be delighted to hear Commissioners' views as to whether that responsibility can be operationalized in any particular way rather than just say we recommend that it is their responsibility. If it's self-evident, we should probably say either why it is, which I think is easy to do.

DR. COX: But I have a comment on this. If we don't make clear and crystal clear what the sort of priorities and goals are, then the investigators are not going to know whether they should come back and worry about it. And Mary Claire said that several times. Even she, as sophisticated as she is, you know, was still trying to go back and forth about really what are the principles and what are the rules. So that the ... I think we should strive as much as possible not to be able to have anyone say that, that they don't understand what the rules are. Because that's a double-edged sword. Some people may not understand what the rules are, but I play basketball with my four-year old, and he doesn't understand the rules for a different reason because he wants to win. So the...and I think it's the same thing here.

DR. MIIKE: I think we have to be careful about these because they seem to be in dark opposition to 7 and 8, because 7 and 8 say let's re-obviate the need for recontact, and yet the following one says they should be monitoring when they should reconsent. So I think....

DR. COX: I think the issue, too, I think that's right, actually. I think the issue here is for us to clarify when the reconsent process gets initiated and how one thinks about that. And when that's not necessary. And 7, 8, and 9 are dealing with it in various different ways. I really think it's that issue and I think your point is well taken, that as just

written down here. That's not clear and I just think we have to put these together. One more suggestion, that is, Mary Claire's example with the tomoxofin will be an extremely powerful example to put in a report, not only the way she handled but alternative ways that one could have handled it.

MS. CHARO: In some ways I'm sorry that Alex had to leave early because he once wrote an article about informed consent that held some lessons that I think are valuable here. If we go back to Mary Claire's protocol in which people have consented to research looking for markers but now in fact we're looking for the actual gene, it was a genuine interpretive question here about whether or not the consent they had given originally was sufficient. And in the article on informed consent, Alex walked through the different points of view from which one could answer the question. Whether a professional would say that this is in fact substantially different is one way of saying has this changed enough. The second way is a more subjective view from the point of view of the patient to hear the subject and ask, would the typical subject feel that this consent had covered this new scenario or would they feel that this was new. And in the law, we've got a very confused set of rules about which point of view ought to dominate, but I do think that in a research context it would be appropriate to conclude as a principle that the point of view that ought to predominate is that of the subject. You ask would a typical subject feel that they had in fact consented to this particular kind of research and use that as your benchmark, rather than the IRB's view or that of the professional. It's different in a clinical setting, but in a research setting where essentially the subjects are doing you the favor of being volunteers, one tends to be more considerate of their subjective viewpoints.

DR. LO: Could I follow up on Alta's comment which I think is very, very helpful. Is the implication then that we need to have a community advisory board and somehow that board is given the choice?

MS. CHARO: IRBs are the role of trying to figure out what a typical subject or potential subject would think, feel, or say. They do it all the time when they look at consent forms and ask, "Is this comprehensible and is this sufficiently informative?" They always do that with the subjective viewpoint of the potential subject in mind. It strikes me that good IRBs frequently ask for a consult when they feel like they're out of their depth, and this is certainly another example of a case where they might want to. But mostly I think it's to remind people there that the shoes they should be wearing when they say, "Is this really any different?" are not the shoes of a researcher or a trained medical

professional. They are the shoes of somebody who is a layperson who is reacting to this, not from the point of view of technical matters but from the point of view of emotional matters. And that's often enough. Hopefully it's most of the time enough. But they do their best. The obligation is for them to do their best to figure out what the typical subject would want.

DR. LO: Again, if I can just take a second to try and flesh this out. Would we then, having said the IRBs, the proper locus, say the IRBs ought to have someone on their panel who's an expert in this kind of genetics research and adequate representative of community or representatives of the subjects of the study?

MS. CHARO: They already have a layperson on there by virtue of the statute.

DR. LO: Right. But we were concerned before about whether one layperson gets drowned by the 33 other professionals working in the institution.

MS. CHARO: A very valid concern, and yet another one for the list of things to worry about in a kind of generic look at the whole system and whether it has the capacity to carry the burdens that have been placed on it.

DR. LO: And again, are we asking IRBs to take on yet another tough issue?

DR. SHAPIRO: I think in the terms of that latter point, Bernie, the statistics, someone mentioned before that 10 IRBs have 48 percent of the protocols, obviously some very large workloads around. It seems to me that there areXputting the resource issue asideXa number of solutions to this. That is, that IRBs that are dealing with that many protocols probably have a lot, or regularly get protocols that have or are dealing with genetic issues or regularly get protocols that deal with human capacity issues in a sense. And therefore there's plenty of room to mobilize your IRBs in a somewhat more specialized way than we often do. Now that's a resource issue; I understand that part. That just leads you back to the resource issue, but it seems to me there's no lack of potential solutions if one feels this is all important enough to put some resources behind it. We have to think of how to do it and so on. And my view on this is if we think it's important enough, my test is do I want, well I suggest we spend some resources; that is, do one less NIH grant because we have to put the resources here or something of that nature, not institution by institution, but it comes out somewhere. You know, that's a test I use in determining myself. Am I willing, is this important enough that I'm willing to forego some other thing we could do with this money? I don't mean institution by institution but as a whole social policy. And if it doesn't pass that test, then it doesn't pass

the test that it's important in my view. Except for once in a while, once in a great while. Okay. There are recommendations 10 and 11. I understand 11 better than I understand 10, frankly. But let's see. Maybe Eric can help us make sense of what we're talking about in recommendation 10. There are two parts of it, and I presume this has to do with, Eric, what happens when using this material for some new project. That's the context, I presume. I can't really quite figure it out.

MS. CHARO: You know, the way I'm reading 10, it actually is not terribly consistent with what proceeded, because of course these were not meant to be consistent with one another. They are truly alternative recommendations. The way I'm reading 10 I understand it this way: Prospective consents can be used only with regard to protocols that are going to involve unidentifiable samples. In other words, you can allow your sample to be put into the great pool of unidentifiable or not. Prospective consents can't be used for future research that involves identifiable samples because we are not going to waive the usual individualized consent requirements. We're not going to let prospective consent trump it. That's how I'm reading 10. Am I understanding it accurately? Can I say that I don't like it?

DR. SHAPIRO: Yes. [LAUGHTER]

MS. CHARO: I don't like it. I think that prospective consents are not a bad way to go. It may be that we want to give some more thought to the idea of prospective consents being used not to eliminate the need for recontact, but to ameliorate itXallow for an opt-out as opposed to an opt-in consent in the future. For example, I contract with you to agree that an opt-out is sufficient. But I think the prospective consents are tremendously useful and in the long run, can make a research endeavor far more efficient. And I hate to hamstring them from the very beginning.

DR. MESLIN: I was going to say, at the risk of trying to move you one way or the other, one of the reasons why we presented that type of recommendation, somewhere after recommendation 8, which was the recommendation that says there are a number of nice consent forms and processes out there that we might want to recommend to people, is just to juxtapose them. We heard from the NHLBI. We heard from NAPBC. We heard from a number of groups whose general and/or tiered consent activities relate precisely to what you I think would like to see. So you might just simply want to reject the concept of

recommendation 10, but I would encourage you to think about adopting what is in recommendation 8 if you want to reject that.

MS. CHARO: But this would be yielding to manipulation by the drafters of this memo.

DR. MESLIN: Well that's why I waited until 10 before.

DR. SHAPIRO: The issue of this consent is what consent is valid for futureXnot completely known at the timeXprocedures or uses of a material is not that different from what we were discussing just a few moments ago in the advance consent. It was a very similar kind of problem. And it's a generic problem and it's worth thinking about as to whether, just how narrow Bernie's example before was, that if we interpret this consent very narrowly, he has a lot of trouble. He may have trouble with it anyway, but certainly if it's interpreted very narrowlyXlet's say MRI versus image studiesXit makes a big difference, probably, to how he would feel. He may not like either, but at least he'd feel differently about one versus the other. And really that's the same; it's in some sense the same issue here in different guise. Just how much can we say that advance still feels acceptable to us? So for example, in the case of Alta, or the proposition Alta just advanced, do we feel that some kind of advance consent which is general, together with an opt-out or something, is really informed consent or at least sufficiently close to informed consent that we would be happy to deal with? I think that's a very interesting issue. Larry?

DR. MIIKE: You know, I want to reintroduce a notion I talked about a while ago, which is that I don't have a problem with giving advance consent or use of my tissues and they know who I am so long as the information that they have is limited in time. I would be very offended if they never contacted me but they were delving into my medical record subsequent to the giving of the tissue. So I'd at least consider a notion of the advance consent about the timing, the time framing, which I understand what I'm consenting to. I can't consent to information that may be generated in the future about me of which I have no idea at the time that I'm giving consent. But I can certainly accept the notion that, if I went in for a cancer biopsy, anything they wanted to know about me in that episode, if they asked me and if I said yes, I would feel comfortable with it. But I would not want them to continually delve into my private life without my knowledge.

DR. SHAPIRO: Regarding future access to your medical records. Bernie?

DR. LO: There were others before; I was just trying to get in line here.

DR. COX: I really agree with that and I really support the idea of this prospective information. It's not really a prospective consent, but it's telling people sort of what the rules of the game are again, that we don't know exactly how it's going to come out but here are the things that are likely to take place. And that's a situation where I can really go for an opt-out, because if people say, "Listen, I'm one of these people whoXbasically I've signed up for researchXthat I'd like to know what you're doing but if you don't hear back from me, go ahead and do it." Now if somebody's already told me that, then that's how they feel comfortable doing business and that they will get information from me so that when I know more, they know more. But it's two different ways of doing it, either getting assent from them or getting them to opt out. And not only is it respect, but it actually has merit to it from the point of view of having better understanding of the people. It gives people options, real options. But my biggest concern is exactly what Larry brought up, because this isn't a carte blanche to go into somebody's medical record whenever somebody else wants to do it. So the original research that you get involved with has to be time limited and/or content limited in terms of medical record entries, which are often enough I believe.

DR. LO: I want to try and see if I can draw together some of the comments which I agree with and I think are very helpful. I like option 8 rather than option 10. And then looking at option 8, I would like us to encourage tiered consent and to discourage general consentXyou can use it for whatever you wantXbecause I think that's so vague as to not really be consent at all.

And I just want to raise a couple points for discussion or clarification. One, tiered consent plus an opt-out sounds good, but we need to keep in mind that using the opt-out too often can be an invasion of privacy if every time they want to do a new study I get another postcard. I'm moving around the country trying to escape from my past and they keep tracking me down, I may not like that. And then I want to pick up on Larry's point. I think it's really important and I think there is a big difference, as he pointed out. But I want to test what the boundaries of that are. So on the one hand you use the sample but not only use the clinical information existing at the time of the sample, but 10 years later using publicly available information from death certificates, look at overall mortality and whether a given gene predicts that. So presumably that would be okay if it's publicly available information. Okay. How about going to a little harder case, cancer registries, and saying that I've given consent in 1998 and in 2000-whatever, 10 years from now,

2008, the investigator says, "Well, I'll go to the local Northern California cancer registry, which has all the cancers of interest in their registry, not going rifling through my entire medical record, but finding out something about me. Does that fall under your invasion? Would you be offended by that?

DR. MIIKE: If I'm dead, I wouldn't care.

DR. LO: But you wouldn't want a researcher to look in a cancer registry for a 10-year prediction of the . . .

DR. MIIKE: That's a hard case. But if they're trying to find me in this registry, then to me they're delving into my personal life, subsequent to the time I gave permission.

MALE VOICE: So you would have wanted them to have said up front, "We're planning . . ."

DR. MIIKE: But obviously there's another issue sitting over here. Do cancer registries, is that my personal information? I don't know.

DR. LO: Well, it's linked to you. It would have to be linked to you.

MS. CHARO: Mary Claire King's research, in which she talked about how ideally she would like to have had survival data, is exactly the kind of research that might require repeated trips to your abstracted medical records over a period of two decades.

And she was doing that research with a single opt-out moment, in which people opted out at the very beginning but were not subsequently recontacted to say, "Well, it's been 5 years and every 5 years we always go and check and see if you're still alive. Do you mind if we go and check and see if you're still alive?" Do I understand you correctly saying that you would like her to have had . . .

DR. MIIKE: How is she gaining access to my medical records?

MS. CHARO: The medical records are being abstracted by somebody who's on somebody's payroll to do just this. They're told which medical records to pull.

DR. MIIKE: I know. But how are they pulling my medical records? How are they getting access?

MS. CHARO: Because you were initially in the study because you did not opt out.

DR. MIIKE: Yes. I understand that. But how are they getting my clinical records?

MS. CHARO: In the first place? How are they getting them? Well, you know, that's a practical problem that varies from research protocol to research protocol. If there is a registry, probably this information is being sent to the registry on a regular basis by all of your various attending physicians because they are all part of the process of collaborating with the registry and you've been collaborating actively because somewhere along the way you said it's okay for you to continue to collect data while you treat me and send abstracted versions to the registry.

DR. MIIKE: Well, that's a different situation where I was actually told that and I said yes. So I would feel comfortable with that. But I would have had the opportunity to say it's okay. It's just the situation where they're accessing information subsequent to my saying yes.

MS. CHARO: Like, for example, recontacting your attending, assuming that you're one of the rare people who has the same doctor for two decades.

DR. MIIKE: Yes. I wouldn't want my doctor to be providing information without their ever telling me that my personal doctor is providing information.

DR. COX: This is a recurring thing that happens right now. When researchers hook up with Kaiser or other situations and Kaiser says, "Sure. We've got a contract with you. You can look at our patients." When the researcher calls up and says, "You know, your doctor said it's okay to call you," not very many patients object, but it only takes one to shut the study down. And that patient then says, "What the hell's my doctor giving you my records for?" On the other hand, if you do this and you say, "I'm calling from Kaiser. I work for Kaiser and we're asking, is it okay to use your records in this study." And people say "Yes. It's fine." And then you go and you ask them questions. So you say, well that's a trivial point. But it's the difference between being able to conduct the research and not, because it just takes one person; that's all it takes. And these aren't theoretical things. These are real things that happen every day right now. And it shuts downXjust 2 days ago I had an example of this in Hawaii. It shut down the study for 6 months.

DR. MIIKE: I wasn't the patient.

MS. BACKLAR: We wouldn't do it any differently in a research protocol with mentally ill people where I'm getting names from the information system and then I have to get somebody from the state to contact them first to see if I can contact them. So it's

exactly the same situation.

MS. CHARO: It's a very commonly misunderstood. People think that review of medical records in order to determine who should be recruited is not subject to these requirements. They're wrong, but this is a frequent misunderstanding I've discovered. But, Larry, your situation's not about recruitment. Yours is somewhat different. I mean, basically, if I understand you correctly, you are advocating that a single moment of giving permission to be a research subject in some fashion, a single moment in time, is insufficient if being a research subject is going to involve multiple requests to your physician to go into your records and abstract them for the researcher.

DR. MIIKE: Let me put it at a gut level. I can distinguish my personal self apart from a piece of my tissue that was taken from me a long time ago. If they continue to look into my medical record on my living self, that's a little different from giving permission. But it's that level that I'm talking about.

DR. COX: Larry, can we ask you a question? What if somebody said, "Listen, what we want to do is we want to look over 20 years for this piece of information."

DR. MIIKE: Well, that's different. Then they've asked me that specific question.

DR. COX: I don't think it's actually the multiple times going in; it's up-front telling somebody what you have in mind of doing. So that's exactly what happens with a lot of these things. You get tapes. They become public tapes of these longitudinal studies, but it's clear what's going to go into those tapes up front. And you don't come back halfway through and say, "Oh, by the way, now I want to actually start looking at an additional X, Y, and Z." I think that's what you're objecting to, Larry, and that's what most people object to. But if up front you could basically say what you're going to be assaying or sampling from the chart, then I think most people . . .

MS. CHARO: Right. But they could have told me when I gave permission like this that we're going to spend the next 15 years going into your chart once a year, looking at your mammogram results, right? And they're doing that, and then along the way somebody suggests an association between breast cancer and abortions, or miscarriages, or years on the birth control pill. And so now, 7 years into this, what they're going to do is they're going to go in and they're going to pull that information. And that is distinctly different, and yet it's part of the same study when they suddenly are thinking, "You know,

we might be finding an association here."

DR. COX: But that's not kosher because basically what you're doing is that you're doing something different in terms of the body of information than you set to begin with.

MS. CHARO: Right. But these prospective consents are written very generally. And the point is do we want to permit these to be written generally enough that people can say, "Yes. You can go in and you can use whatever you want over the long term." Or are we going to prohibit people from doing that because we think it's so far away from . . .

DR. SHAPIRO: The big difference here, whether we're dealing with identifiable or nonidentifiable cases, nonidentifiable are not a hard, nothing very hard for me. We don't have to spend any time right now. It seems that we're dealing with the identifiable cases. And my own view is there are limits to this prospective consent, and they're pretty stringent. And that is that you can't justXI mean I can't quite imagineXthere's a certain amount of tiered consent you can do at various times I'm sureXand we'll look at what some of the people attempt to doXbut there are limits there because if you're going to have the kind of permission that lets you go back into the medical record, that's a serious matter, a very serious matter. Go back without reconsenting. Let's see hereXBernie? Bette? Bernie's had some chances. Let's start with Bette.

MS. KRAMER: I'm confused. I had thought that the proposal was a prospective consent for continuing use of the sample, but that that did not include consent to continue to access the medical record.

DR. SHAPIRO: I think that's an open issue. That's a question of how we want to, how that original consent is structured. It could be structured either way in principle.

DR. COX: And that's what we're saying, Bette, but then there's a coda on that that if you tell people up front that you're going to access the record and for what, then it's a bounded thing in the beginning, and people get a chance to consent to it or not consent.

MS. KRAMER: Yes. But they're two very different cases. And I think we need to distinguish them.

DR. MIIKE: You know, Bette, I would say, "Yes" if they said, "We want to follow your case and the medical record for this specific issue." But if they say, "We want access

to your medical record indefinitely to do research," I'd say no. I'd say you have to come back and tell me for what reason.

MS. KRAMER: That's the third distinguishing . . .

DR. SHAPIRO: Right. That's not consent in any way. It wouldn't qualify in my view. Bernie?

DR. LO: Realistically, I think what we're going to do is reinforce the tendency to develop large cohorts specifically for the purpose of doing research, so this is a take-off on FraminghamXHeart-Lung, which is doing this. There are other large prospective studies because, in point of fact, the information I really want to get is not in your medical record. I want to come back and ask you questions about various genetic conditions, family history that probably I can't get at through the computer. And realistically, I think what we're going to be seeing is these ongoing studies where you agree to be contacted on a yearly basis and they ask you, "Is it okay to ask you these additional questions?" or to do this or that. Sort of the prospective, ongoing nature of the followup is built in. I think ethically, that's much more acceptable because there's that ongoing interaction that means you're not doing things that people didn't understand and didn't consent to. And frankly I think for the researchers, it's a better design because you get the chance to ask the questions you want to ask rather than having to hope that it's in the chart that was there for other purposesXbut that's more expensive. And you've got to realize that. To put together these cohorts costs money.

MS. KRAMER: But that's like I said before. We do longitudinal studies like that where you go back every 8 months, every year to follow a subject over time. It's part of your research plan.

DR. SHAPIRO: Okay. There have been some helpful comments, but let's move on here to look at recommendation 11 here. Eric, do you have any comment on that?

DR. MESLIN: I think this is a bit more straightforward than 10. We're really speaking about prospective collection and the requirement to obtain an informed consent in order to use that sample. I may just say in passing that, having heard the conversation about essentially recommendations 7, 8, 9 and 10, one way of getting to Bernie's helpful question about tiered consents, is that we could summarize these

concepts in one or two recommendationsXone relating to what we are expecting in the prospective consent process, both in terms of the forms that may be developed and how specific we would expect those forms to still qualify as consent documents and how general they would be to still permit use of those samples without an opt-out. The Commissioners have mentioned that there are examples where individuals have indicated that they would be prepared to have their samples used, but the more uncertain you are about what is going to be done with them, the less that should count as prospective consent. And we haven't set that boundary.

Recommendation 11, which could have occurred earlier in the list because it's supposed to be a bit more straightforward, is simply meant to indicate that this is the best-case scenario, the prospective collection of information from a sample, use of a sample whether stored or collected, where the information can be linked back to the individual requires what we're calling full informed consent, and that's the informed consent we're all familiar with, a listing of risks and benefits and the like from the regulations.

MS. CHARO: I do have some difficulty with some of the language that's being used in this to express its ideas. I find myself uncomfortable with the parallelism between a sample that's linked to an individual being made parallel; that is, his identity is not concealed from the researcher. The identity probably is concealed from the researcher. It's probably coded. And so I think that that particular sentence actually offers the possibility of a fresh round of confusion. I'm also uncomfortable with the phrase "full informed consent." I found myself scribbling, "as opposed to partial." Now I can, however, understand that informed consent as opposed to a mere opt-out might be what you have in mind but would like to again suggest that these phrases might be confusing.

DR. MESLIN: Well, your point, Alta, is that it's largely editorial. It's not that there's a conceptual confusion. The language is saying "full," which I believe we understood to be....

MS. CHARO: Well to be honest, I wasn't sure what this meant until you just explained it because the language was so confusing to me I really wasn't sure what the agenda was behind that particular recommendation. I read it four times and then just left it in red.

DR. SHAPIRO: Are there any other comments beside with respect to what is marked here "Recommendation 11"? The other ones that are left here are reallyXI don't

know if they require any discussion right now. We'll have to wait. They're really just . . .

DR. LO: Before we move on, recommendation 11 seems to restate what's the current situation, that if it's identifiable, right, not linked, you need informed consent. Conversely, I guess, do we want someplace to affirm that, if you have a sample that's already been collected in the past and you're going to be using it . . . I guess I'm asking a question. For all these stored pathology samples that are currently in hospital pathology departments that now are linked to somebody's medical record number, are we going to allow those samples to be used if they're given to the researcher in an unlinked fashion? If the pathologist just says, "I'm going to close my eyes and take 150 samples of Cancer X and I'm not going to know whose they are and send them off," we're going to allow that. Bette says no pathologist would ever do that because they're such compulsive recordkeepers. But if they were, are we going to . . . The question keeps coming to me. We heard a lot earlier about this is a valuable resource, there's a lot of good research that is done on that, we shouldn't sort of throw that away. I want to try and be as clear as we can about what are we going to allow to be done with those archived samples?

MS. CHARO: If they're given without identifiers or if, as Mary Claire King did, the links in those codes are severed irrevocably, it's my understanding that we were comfortable with the current rule which says they can be used with impunity.

DR. LO: Okay. So you were saying it's not how they're stored in the archive, it's how they're given to the investigator.

MS. CHARO: It's whether or not the individual is identifiable. It's neither how they're stored nor how they're given. It's whether, in the end, the individual is identifiable. That's the real question, is whether or not the donor of the tissue could ever be identified. And a severing of the link is one way to make that individual unidentifiable.

DR. LO: Okay. For Bette's pathologist, to make this work, the pathologist at some point has to delete the code.

MS. CHARO: That's right. That's another way of making them unidentifiable. By the way, since Bernie made us go back to 11, let me just say that it's actually written a

little over-broadly the way it is, because it does not include the exemptions and exceptions that currently exist. Not the exemptions, sorry, the exceptions that currently exist that permit a waiver of consent.

DR. SHAPIRO: Any other comments on this? With respect to the remaining ones, I'm . . . It doesn't seem to me that we need any real discussion right now. These are kind ofXI hate to use this wordXbut they're little sort-of "mop-up" suggestions here, which we will get to, but there's more important issues to deal with. It's not that they're unimportant. So I'm just open for any observations, suggestions you might give.

MS. KRAMER: Harold, a question. Back up a minute to the last issue. Wasn't that one of the cases that Dr. Hook talked about at the last meeting, where the cohort that was givenXI'm trying to remember nowXwhere the cohort that was given was small enough . . . I guess it would depend on whether or not the repository or the pathologist in question was willing to destroy any record of the samples that they were given. Do we know practically whether or not that would happen? Alta, is there any legal liability on the part of a repository to keep a record?

MS. CHARO: Well, I don't know the answer to that. But I can tell you as a lawyer that if they hadn't kept a record and there was a reason why it would have been helpful and it turned out somebody was harmed, I'd make a good argument that they should have kept it.

MS. KRAMER: Yes. I'm just thinking about that. I wonder if any pathologist or repository, in fact, is going to destroy a record of whose samples.

MS. CHARO: I think more realistically what will happen is what Mary Claire King described. The repository has the samples listed under a set of codes. There is Code A, B, C, D, and E. And they will take those and they will give them a new code, 1 through 26, and they keep a little record that says, "A equals 1, B equals 2," and they give 26 samples to the researcher that are labeled 1 through 26 and the researcher uses them. Would this repository ever destroy the record that says, "We gave away samples A through Z"? Probably not. Might they destroy the record that says, "A equals 1, B equals 2"? Yes. That's what she did. And by doing that, they know as a group what was given out but they cannot do a one-to-one correspondence between a specific sample and the results the researcher found and the particular donor of that sample. That they would do, and they'll do with some hesitation because of the possibility there would be some day some valuable reason to link back to the donor. But they will do it.

DR. SHAPIRO: And if they don't, it just means another set of protections gets initiated. It doesn't mean you don't go ahead. It doesn't mean anything of that kind. It just means another set of protections comes in. They're now identifiable and you go down that road, that's all.

DR. COX: But you see, one of the things that we haven't stated here yet that certainly isn't in the common lexicon of most people is the possibility that things are identifiable. But, it's that when it goes to the IRB, you have approaches in place that say that that information won't go to the researcher. And what that does is lower risk than if you don't have those things in place and you consider it differently. So I think, just because it's identifiable, the research community does now, it's identifiable. Then everyone has that stroke. So it could be under different . . .

DR. SHAPIRO: Yet another harm.

DR. COX: Yes. Exactly. Stroking our researchers. But I think that . . . So then they go to these extraordinary efforts to destroy all the links. Well, I don't think we necessarily have to do that.

MS. EISMAN: I'd like to address that point that Bette asked because it was a point that Tom Murray asked me to address after the last meeting. And I did do a bit of research, not comprehensive research, but did talk to a few repositories about their practices for dealing with unlinked and coded samples. And I think David Cox yesterday made the very good point that it does appear that the vast majority of samples are used in a coded manner, not in an unlinked manner. And that is actually more rare than I even expected it to be. A lot of repositories don't destroy that link and they know who the samples come from, but they do also have a . . . some of them also do have a statute that, when they send out samples to researchers, the researcher can't come back and get any more information.

So even though the repository knows that Sample A is John Smith, when they send it out to the researcher, the researcher can't come back and get any more information than was originally sent. So whether that's considered coded or linked is one question. The other question is about unlinked samplesXthat in most cases there is a list kept of who those samples came from. So if it's 50 people, there is a list of those 50 people that the sample came from for a number of reasons. The main one that was cited was quality control. They need to know who those samples came from because, if the researcher came back and said, "I need 50 additional samples completely different than what you first sent me,"

if they don't know who they came from, then that repository can't function. So those are a few points I wanted to make.

MS. KRAMER: Then what does that do with the definition that we accepted, that if, no matter how far-fetched it is, if there's anybody who can link, anybody who can identify who the samples came from, then we're calling that identifiable?

MS. CHARO: It is. Because it can be done and a circumstance will arise where somebody wants to take advantage of that. You do the breast cancer studies in one of these settings where you've maintained the links but everybody understands we're never going to let the information go back to the donors and we don't care who they are. And suddenly you discover that people that have the breast cancer gene seem to be at high risk of ovarian cancer, or the next thing it's going to be is that they're at high risk of developing a third eye, whatever it's going to be that seems to be linked. And suddenly somebody says, "You know, it's absolutely imperative that we send this information back up to the donors because if they get it now, they might be able to get some kind of preventive strategy going." That is why you have to understand that these are identifiable, because as soon as that temptation arises, you're going to have a discussion about whether or not the information is sufficient, is the cure worse than the disease, is the information too ambiguous? That's why you have to understand it being identifiable.

DR. COX: But, Bette, let's go one step further from what you're saying. What are the implications of it? This comes in my view what Harold was saying earlier about needs to go before an IRB. By basically saying these are identifiable, it says that they go before an IRB.

That doesn't say what kind of hoops people have to go through, so that they go before the IRB but the IRB says, "You say you're not going to ever give information back to the researcher? Sign in blood. Sign right here." And then when the researcher comes back and says, "Well, but I really have to go back," you say, "You see your blood right here. You can't do it."

DR. LO: I understand the rationale for keeping a list of who the 50 samples were so you can send them a fresh batch. What's the rationale for keeping the code that A equals John Smith if David Cox has made people sign in blood they're never going to backtrack? Why have it? What's the rationale for keeping that?

MS. EISMAN: That's a good question, and I didn't get that in the answer when I talked to the people at the repository. The answer was that that's how they do it. I'd be

happy . . .

MS. CHARO: It is so that people can go back or so that they can do subsets. For example, you sent me 50 and I looked at them and there were 10 there that have a characteristic that's interesting to me and I want you to send me 10 more of the same. Well, they've got to know which those 10 are. You know them as numbers 17, 29, 33, etc., and they've got to know which those are so that they can go back to the blocks and figure out where they've got to get another section.

DR. LO: Right. But then that violates the signature in blood they gave David Cox because the agreement was I was never going to go back about the subjects.

MS. CHARO: And indeed, David, you and I are talking about different kinds of risks. You're talking about the risk of invading the medical record or the tissue for more information. I'm talking about the risk, quite the converse, of sending information back down to the donor, which are two very distinct kinds of risks.

DR. COX: In both cases you're going back. Bernie's absolutely right that they're different risks. And that's what we need to do, is talk about what these different risks are in different scenarios. Not to try to make them go away by taking something that's identifiable and pretending it's not.

MS. CHARO: This is where, to coin the horrible phrase, how it's used by the researcher begins to get valuable, get very important, because what I want them to sign in blood is that I have absolutely no intention of sending information back down the line to the donor. Now we all know that situations can arise that cannot be foreseen now. By definition, unforeseeable things can't be foreseen. So, hey, there might come a circumstance. But I have no current intention of going back down the line. And so long as that link is maintained, that possibility is preserved. Now if you put into place some kind of system on which we have a filter so that when the investigator says, "I think I've found something that requires me to go back down the line and tell the donor," there's another body of people who say, "Well let's talk about this all together." Whether it's the laboratory's own group or it's the IRB or it's some neutral body, that acts as a check on that particular kind of risk being realized, and is exactly what may allow something to be a minimal-risk procedure even if it involves looking at stuff that is potentially stigmatizing or embarrassing, because you've put into place a series of protections against that information ever getting out.

DR. SHAPIRO: I think it's really quite important to keep on reminding ourselves that, just because it's identifiable, doesn't mean a ton of bricks comes down on the study. That's not what it means. It just means now there are other things to think about and you have to start thinking about them. They may be very small, in which case they'll be dealt with in a very simple way. They may be very difficult, in which case you will have to go through them.

DR. COX: But when you have the research community being involved with thinking about these things, that's going to be very useful because no one has more at stake than they do, at least from the point of view of carrying on business. Patients have a lot at stake. But what you'd like is for the research community to have something at stake here, too.

DR. SHAPIRO: Any other comments? Are there any comments, since we are going to adjourn in a few minutes, are there any . . .

DR. MIIKE: Yes. What does recommendation 11 mean? Do they have to get informed consent or not?

MS. CHARO: Unless they meet the conditions for a waiver.

DR. MIIKE: But for that example, where a repository is the only one that has the code, that the researcher doesn't, we're calling that identifiable and we still have informed consent?

MS. CHARO: Unless they meet the conditions for a waiver.

DR. LO: So if it's not greater than minimal risk and it won't adversely affect the welfare of the subject, you don't have to get consent.

MS. CHARO: And it's not practical to get consent.

DR. MIIKE: Okay.

DR. SHAPIRO: Then we agree that this is one or something or at least further up the ladder. Okay. Before we adjourn, is there anything you'd like to say now? We will have to come back to 12, 13, and 14. They have their own importance. I don't want to minimize them, but I don't know if we can productively say much about them today. Let's see what comments there are so it would be helpful. Bernie?

DR. LO: Yes. I'd just like to say this was really a very productive meeting. I want to thank you, Harold and Jim, for sort of leading us through this. And to Eric and the

staff for really sort of allowing this to happen. I think we've made a lot of good progress, had a really good discussion. I think we're getting closer to our final product.

DR. SHAPIRO: Any other comments? Well, thank you very much. It's been a long day. We almost began at 7:30; it was actually quarter to eight. It's now 4:30 almost, 4:25. So thank you all very much and let me extend my thanks also to staff for mobilizing this meeting and, Trish, thank you for encouraging us to meet here. It's very nice to be out here in Portland. We're adjourned.