



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

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DR. GUTMANN: Welcome back everyone. We are moving on to the next topic on incidental findings, and that is a discussion of the ethical management of incidental findings in the research context, and Christine Grady will begin our discussion for us. Christine.

DR. GRADY: Thank you. First I want to recognize the other members of my working group, Nita Farahany and Nelson Michael. And Nelson isn't with us today because he has been deployed.

And we also had wonderful help from the staff, Lizzy and Karen and Kate in particular, but lots of people behind the scenes that I don't actually know.

So there were a number of things that we came to agree upon. One is we recognized the increasing possibility in certain modalities used in research of uncovering things that are heretofore thought of as incidental.

So in the increasing use of genetic sequencing and imaging, increasing research with of specimens, using those modalities to recognize it is not only possible to predict that incidental findings might arise, but some evidence might be available about the meaning or implications of those predictable findings and that evidence, such evidence will help to form an evaluation of the extent to which the incidental findings provide useful information as to potential net benefit to participants as opposed to say uncertain information or information that might cause unnecessary stress, unnecessary cost, or more burden than benefit.

So based on the ethical principles that we have been highlighting in a number of other areas, we thought that researchers should develop a plan for managing what we call the predictable incidental findings and for disclosing to participants those incidental findings that are known to be significant and actionable, and when relevant analytically and clinically valid or the equivalent of those things.

This plan that the researchers put together should be reviewed by an IRB and approved, and should be described to participants in the process of informed consent including what type of incidental findings might be found, whether and how they will be disclosed and how participants might opt out of receiving certain types of information.

There are a couple of things that were really important about our discussion when we were thinking about this.

We wanted to be sure that predictable is not synonymous with common. That there may be things that you might predictably find even if they are uncommon, but they could be serious and actionable, and things that you would want to do something about.

We also wanted to be sure I think that predictable is not synonymous with has to be disclosed.

So there are things that we can predict that you will find, you know, there are lots of examples that I could give.

The researcher needs to have a plan and say which of those he or she will inform participants of.

We debated, as the earlier group did, the extent to which participants might exercise the right not to know certain findings, and whether there might be circumstances in which researchers could or should override participant preferences not to know.

And we debated similarly are there times when participants may want to know something that a researcher can or should decline to tell them. So those are the same questions that Dan raised earlier.

They are slightly different in the research context than they are in the clinical context so if we can come back to them.

Another thing that we recognize, everybody is aware that the ACMG recently recommended that clinicians who are running large scale genetic sequencing should look for and disclose a delineated set of variants that are sufficiently serious to patients who have the sequencing done.

Other groups, and there has been quite a number of really good literature, groups of people who have spent time thinking about the implications of incidental findings and research, and many of those groups have proposed approaches of trying to group incidental findings into categories.

One category of findings that should be disclosed, another category of findings that might be disclosed, and another category of findings that ought not to be disclosed or some other way of describing them, but bins like that, and several groups have come up with this kind of an idea.

The differences between the three groups are based on the confidence that one has in what the finding means, and an evaluation of the net benefit of disclosing the finding to a participant.

So we thought, as a working group, that it would be advisable for knowledgeable representative groups, including subject matter experts but not limited to, to define or try to -- define is the right word, the types of incidental findings that might predictably arise in each of these research modalities.

The group should assess the available evidence of their significance and actionability, and then develop lists that would guide researchers and IRBs regarding the kinds of findings that should, might and should not be able to be disclosed to the participants.

We thought these lists ought to be evidence based, accessible and updated in the group's representatives. And the groups might have identified specific areas where additional research was needed to establish evidence of significance or actionability.

We thought having such kinds of lists or groups would be very useful for researchers and sponsors as they plan, develop their plan for management of incidental findings and also IRBs and other oversight bodies who are reviewing the plans.

We did recognize as a group that this kind of categorization may be more difficult for the modality of testing biological specimens than it would be for sort of genetic sequencing, for example, only because of the realm of possibilities for biological specimens is so broad.

A third finding group recognized that research is different than clinical medicine or clinical care in that the primary goal is the development of generalizable knowledge, and there is a broad spectrum of types of research in which there are differences in expertise, and that there are considerable costs and burdens that might be involved in looking for incidental findings.

So we concluded and proposed to the rest of the group that researchers do not have a general duty to look for incidental findings, however, a researcher could adopt, with IRB approval, a plan that includes looking for selective findings and selective incidental findings of predictable kinds of incidental findings.

Now, after this morning's talk I am wondering if some of these uses of incidental findings need to be changed. We used different language as Erik suggested because the predictable incidental findings are not the stumble upon findings.

A fourth finding of our group was that even if a researcher has a very well thought out plan for things that might be predictable and no affirmative duty to look for

incidental findings, he or she still might encounter unanticipated findings, unanticipated incidental findings, and in this case ethical obligations still apply.

So in this case we thought researchers should have a plan in place for this kind of possibility as well and inform the prospective participants that such unanticipated findings could occur.

Then we thought that the researcher who encounters such an anticipated finding should assess its significance, and that to the extent needed seek help or consultation from other experts in order to do that.

And then if the finding is determined to be significant and actionable the researcher should propose to the IRB or to another appropriate specialized oversight body, because some institutions have particular ones for incidental findings, and then an action or a plan to offer participants the option of learning about the incidental findings.

So I think we have several questions for the group. One, just if you agree that if the researcher is to develop a plan for predictable findings, that the researcher should disclose incidental findings that are significant and actionable, that these plans ought to be described to prospective participants, that participants should be given to the extent possible, and this is something to discuss further, the right to opt out of knowing.

Expert groups should gather to recommend the kinds of findings that should, that might and that should not be disclosed given certain diagnostic or research modalities, that the type of evidence needed to inform these recommendations, analytic, validity, clinical validity, seriousness, actionability are the right kinds of evidence, that researchers and sponsors do not have a general duty to look for things that are not the target of their research, but could specify in advance particular things that they want to look for that are outside their target, that researchers

are responsible for appropriate and professional responses to unanticipated findings, might or maybe usually would seek help in verifying or establishing the significance of those findings and should propose a plan for informing participants and have that plan reviewed by the appropriate oversight body.

So I want to just raise three other things that the group didn't discuss, that I have been thinking about since we had our last discussion, and some of them were based on this morning's discussion as well.

One is we talked about the issue of disclosing based on certain criteria like established evidence of validity and significance and actionability, but we didn't talk much about what, if anything, after disclosing we might be responsible for, and that question came up this morning.

Another thing that we did not talk about as a group, but I think is very important, is this issue of filtering because there are some references in the literature to things like okay, one way to avoid the moral obligation of returning findings is to anonymize the data.

Now, that has some costs associated with it so I don't know if we need to discuss that at all.

Then the third thing that we did discuss a little bit, but I want to put in just a slightly different way to ask the question, is the limits of informed consent, the role of the participant, and we did raise the question, the question has been raised about can a research participant say I don't want to know any of these findings regardless of how serious they are or can a research participant say I want to know everything regardless of how trivial it is.

I noted that in some of the work that has been done, primarily in the European groups, that they all say informed consent can or should be overwritten because of professional

obligations, but a discussion in research is just by its nature different than the discussion we had this morning in terms of the role of the physician.

So I think these are things that we need to discuss certainly. Did I miss anything?

DR. FARAHANY: Thank you, I think that was great. I have a couple of thoughts on that.

So first, Christine, I think you did an incredibly nice job of summarizing what we have discussed and a lot of the issues we have outstanding, but also thank you for just the privilege of working with you and Nelson on this, it was truly a wonderful experience in working through these issues.

I agree with the idea that we have some of these issues that are outstanding coming from the clinical research side. I do want to focus on our research finding two for just a moment, because this is one that came about much later in the process for us, it sort of flowed out of our discussions of the other three.

And the way that we are discussing it right now isn't, I think where I ended up on it exactly in just the following way.

So we felt like it would be incredibly helpful to have people who have knowledgeable expertise in the different modalities of research to define types of findings likely to arise. And to assess the evidence for, and then I want to say dot dot dot because this is an area that we find a couple of things that we thought might be useful, a couple of metrics.

We wanted to draw from existing work that has really been done in this area, but I think it would be useful for us to come up with some of the criteria by which we think followed that dot dot dot.

So we said potential significance and actionability, but I don't think what we were asking the groups to do were to develop recommendations about findings that should be returned, might be returned or not, but instead to provide something a little bit more like what we were talking about this morning, if there are secondary findings one can anticipate -- being able to know what the primary secondary findings are that one might anticipate in different modalities, and then be able to put those on a matrix to say, these secondary findings that are likely to arise are clinically significant and actionable.

For then researchers to be able to use that information to develop a plan. So rather than advising them what their plan should look like, to have useful data for them to be able to then rely upon in developing a plan.

And so we didn't opine specifically about which one should be returned or shouldn't be returned, et cetera, and didn't, I don't think come to the position of thinking that we wanted industry groups to do so, but instead to provide meaningful criteria.

And this aligns in a way, because things that are clinically significant and actionable are the ones that we would most likely expect the plan would have some way to address and to return. But we weren't asking, I don't think, exactly for that, but correct me if I am wrong, Christine, if your understanding was different in what we were proposing the expertise weigh in on.

So I put to the group this one in particular would be really useful to have some additional discussion about, but also if there are additional metrics that would be particularly helpful in guiding researchers in developing a plan besides actionable and significant.

DR. GUTMANN: So Nelson is not available, so we will begin with questions, and I will recognize Barbara.

DR. ATKINSON: Thanks. Good report. I just want to be really clear on the no duty to look for incidental findings one. You made that as a flat statement so you really decided that there isn't a duty because what we heard in a lot of people that came and presented is that in a lot of studies they will do a CAT scan of the brain, for instance, and have a graduate student read it for some very specific thing, and unless you have a radiologist over read it you wouldn't know that there was a brain tumor or a malformation.

You really decided that as long as they were careful to disclose to people that they either were or weren't looking for incidental findings it is okay not to.

I've always been a little uncomfortable with not at least saying there are a couple of things that really should be looked for in a CAT scan of a research study, but it would be a huge added cost so I wanted to make sure you discussed it in that kind of a way.

DR. GRADY: I will tell you what I understand we agreed to, and Nita may disagree. Let me use the example you used to play it out. So in that example, as I envisioned it the researcher who is doing the study would have to have a plan for what would happen if there was some unusual finding on the image, let's say.

The plan might include, you know, verifying it with a clinical expert or something like that, but it would not require the researcher to say in every case we are going to do a clinical scan unless for some reason he or she wanted to, and then they could make the case and have that approved by the IRB.

I think the third sort of idea we had is first a plan for, there might be things that you find on all kinds of images that we want to do something about, but then there might be something that we didn't anticipate and then we still have to do something about that as well. Does that comport with what your?

DR. FARAHANY: That is exactly right, which is, you know, one, two and three really go together.

So you have a plan first and foremost, that is the most important thing, you have a plan for dealing with these things and you communicate it to research participants, but if you have a graduate student who is looking at a scan and sees nothing other than exactly what is there, and your plan doesn't say that you are going to screen for secondary findings and put it through additional clinical scan, and your research assistant, your graduate student is competent doing the research that they are actually doing, then there is no duty beyond that to look for and try to seek out additional incidental findings which you didn't stumble across.

DR. GUTMANN: Let me just on this, and I have Jim and Dan on the list, express a very narrow, but I think significant reservation/modification.

So everything, all of the proposals are admirably, you know, policy, practice based proposals which I think are -- so this is my real agreement, which I think is in keeping with trying to minimize the adhocness of the stumbling on an incidental finding.

So you try to create as much both prior consent and understanding and also as much rule based regularity to what happens, and I think that is all to the better.

My small but significant reservation is the narrow case that cannot be avoided entirely, which we discussed at the earlier meeting, of a competent researcher who is competent

to see and analyze an incidental finding that was truly unexpected and knowledge of it would be lifesaving.

That example is no longer in the -- it is a researcher, and the researcher's general professional obligation isn't to do it, but it falls in the category when it is really extreme and really competent of the duty to rescue, if you can.

And there is nothing here that suggests that just a very simple, narrow moral duty, not legal duty, but moral duty, ethical duty, which doesn't, legal doesn't follow, but ethical duty, you find something, you didn't expect, no rule prepared you for it, and if you don't tell the person who is identified that she has this tumor that is treatable this person is going to die and there is nothing in here that says a researcher just like any person, competent person, really in that case has an ethical duty to report the findings.

DR. GRADY: So maybe we should state it more explicitly, but we did, in fact, have that in there.

We stated, what we said was there should be a plan for a serious and actionable secondary findings or whatever it is going to be called, and you still have an obligation if you find something that you weren't expecting.

The only thing that we built in there was if the person who finds it is not either competent to or confident in his or her judgment about how significant it is then the plan should be to have a consultant, and then in the language I think we want to be clear that if it is serious and actionable --

DR. GUTMANN: So it is in there?

DR. GRADY: Should be disclosed.

DR. GUTMANN: Okay, it is in there, okay, then that's --

DR. FARAHANY: One caveat. So this is four, you are stumbling upon something that you really didn't expect to find, it is something that raises concern for you, you may or may not know yourself whether or not it is something concerning, you might assess it yourself or if you aren't sure you pass it along and seek consultation on that model, but your plan addresses this as well.

So your plan says if we come across a serious unexpected finding here is how we will handle it so that the research participant understands it.

DR. GUTMANN: I think that is excellent.

DR. ATKINSON: Maybe make that a little clearer because it addresses my concern on that.

DR. FARAHANY: And they can opt out. So that is in that language as well, to say that it gives an option to achieve the results unless they refused.

DR. GUTMANN: As long as that is doable, that is thoroughly ethically, defensible and absolutely parallels our earlier discussion taking our accounts in the research realm.

DR. GRADY: I think the opt out question is the one we had trouble agreeing with, and I think there are a subset of cases in which, I guess I feel pretty strongly, that people shouldn't have the option of opting out.

DR. FARAHANY: And we just disagree on that.

DR. GUTMANN: Let's come back to that to see if we can as we did in the clinical context parse it finely enough so we can agree, because we did get there on the clinical context.

I suspect we might be able get there on the research context as well if we parse the cases as finely as they have to be parsed in practice. But I really want to be able to get Dan,

Barbara and Jim. Jim, you were first, and then Dan and then Barbara.

DR. ATKINSON: I am okay.

DR. WAGNER: It is largely Barbara's question, but I want to make sure she and I understood the answer in the same way. In her particular case where there is a graduate student looking at the data, is it fair then to say, well, as part of my plan I cannot define any types of findings that are likely to arise, and that is that?

DR. FARAHANY: If it is true, but that is where industry, I am sorry, modalities specific guidance would be really helpful. If you say when you look at the brain there is no chance you stumble across anything different.

DR. WAGNER: Yeah, I think, and I think you talked about this knowledgeable representative group, is that what helps cover that situation where you tell some graduate student I want you to look at this image, coordinate X and Y, and if it has a brightness above a certain threshold it goes in this column and if it doesn't in that column, next image.

DR. FARAHANY: Right. We are not asking, for example, and I use the brain because that is one of the very complicated areas. So if you have a graduate student who is trained to look in the small region of the brain, and you are asking them to just look for the changes in activation patterns in that particular region, and there is nothing else that they see and a competent researcher would see that would give them any pause and cause for concern.

DR. WAGNER: That was the question, competent researcher. Is there an obligation to put together this knowledgeable representative group so that we ensure there are knowledgeable researchers involved in the plan, even if during the execution, we are using technicians or --

DR. FARAHANY: This is a plan that we said should be approved by the IRB.

This isn't just a research and development without any oversight, and it can't be a graduate student simply lacks competence beyond knowing this thing, it is something that arises regularly in the course of research in the specific area that they are looking at, it is something that a research associate should be trained on as well.

DR. GUTMANN: So one of the reasons, this is not a question, this is just trying to put these proposed recommendations in the larger context.

One of the reasons it is so important to recommend what this sub group is recommending about knowing ahead of time and informing research participants ahead of time is increasingly the line between research and clinical practice is very blurred, and even if it is clear in the researcher's mind, which it often is, that this is research, often participants who are getting their brain scanned, are getting their genome mapped or you name it, in a research project some of them have the expectation that if something abnormal is found they will know about it, and some of them don't, but if you don't actually take the time to have a plan and educate the participants you have no right to assume that participants understand that they are just in a research project because it is just those lines, particularly over the last decade, have become so intertwined, and there is so many research projects that quickly morph into clinical.

And so I think these recommendations make that very clear in a way that would not mislead, would minimize the misleading of research participants. Dan.

DR. SULMASY: A rather small point about your fourth recommendation, if I heard you correctly, that after the investigator either characterizes the lesion in himself or herself and if not refers on to somebody else, that they would then go to the IRB to develop a plan to disclose. And if that is the case it seems to me that that is sort of overkill and that we might have an IRB approval plan for disclosure and not involve them again in the point of disclosure. Is the

later what you were saying?

DR. GRADY: I think that is fair. The researcher has to have a plan to begin with that the IRB approves, but we are envisioning that there is a finding that is outside the realm of what they planned for and that there might then -- might not need to be mandatory, but there might be a value of having an independent body look at it and say, yeah, this is something you should return or this is how you should do it.

DR. SULMASY: I might suggest something like that, that the plan ought to be good enough that people be able to have the IRB approve their plan for disclosing those incidental findings, and they certainly would have to report it on whatever disclosure basis, or whatever to the IRB of having found these specific findings, but I would tend to have each time there is something incidental that is found get another level of IRB approval, just be interested in bureaucratic parsimony.

DR. GUTMANN: Can I see the nods to that, because my one concern is that we not make this so burdensome a process for research that it unintentionally dramatically slows the research process down, and I think Dan's is a friendly amendment that you don't have an obligation on every case to go back to the IRB, regulatory parsimony, yes.

DR. FARAHANY: I think that captures exactly for what we intended. There was one piece that wasn't captured in what we said. We meant for this to be an in the plan.

So prior, when you have your full plan approved, the IRB signs off on your plan for unanticipated findings that you stumble across. But there are some close call cases where it would be useful to have an ethics consult, and it is not that it is mandated but like Stanford, for example, has the ethics board, it would be useful to be able to go to them and say this is a close case, can you give us an opinion as to whether or not this should be returned, and that is what we

were trying to capture by that second part, not to make it mandatory, but that it would be a useful thing for institutions to have to provide that kind of ethics consult.

DR. SULMASY: Yeah, that might be a research ethics consultation rather than an IRB under those circumstances.

DR. GUTMANN: Everybody is nodding to that so I think that is a friendly and useful refinement. Good.

DR. GRADY: Although, just to channel Nelson, I think he felt it could be IRB, it doesn't have to be, but it could be.

DR. GUTMANN: That is consistent with the friendly amendment that it could be. But when you make an IRB have to be, you not only burden the researcher but you burden the IRBs, which have huge loads.

Other questions or comments from anybody including anybody in the audience? Our audience has been the source of very good feedback.

Karen Gallinari. Karen, who is a JD at the Montefiore Medical Center in the Bronx, New York, the director of regulatory affairs for research and the co-chair of the biomed working group of the ethics key function group of the 60 USC TSAs. Terrific, welcome. Does this Commission plan to or can it consider facilitating the commission of qualified economists to calculate the cost of and potential impact of implementing its recommendations on incidental findings in the research context as was just proposed for the other group, right, in the other context? So, good question. So just to summarize it, is there an analogous proposal in the research context of calculating the cost of a potential impact of implementing recommendations on incidental findings, and I will let the group respond, but just to preface it, I do think that these recommendations are on the face of them less costly than the recommendations in the clinical

context. They are taking into account that the goal of research primarily is not the same as the goal of clinical, but with that I am just prefacing an answer to the question from Christine or Nita. Nita, go ahead.

DR. FARAHANY: We talked quite a bit about the impact on researchers and the impact on the research enterprise and really sought to balance the research enterprise being able to progress with finance and respect for individuals who are participating in the research, and felt that the primary additional burden that we are placing on our researchers are ones that they already, in many cases, undertake, which is to have a clear plan which communicates and addresses how they are going to think about and address incidental findings and return that information.

So I don't think it warrants the same kind of economic analysis that the screening programs that arise in clinical settings do. So we considered and didn't feel like it was the kind of burden that required and called for economic analysis in this area, but certainly I think it is always useful to invite other groups to undertake those types of economic analyses and to consider the cost and benefits of different programs.

DR. GUTMANN: Another way of thinking about it, on the face of it, it seems like it would be more costly to ask for an economic analysis than it would be just to do this, because there is a cost of calling for economic analysis, they are not without.

And this on the face of it doesn't seem to call for it because it is just adding clarity and some specificity to what researchers have to do anyway before they go to an IRB.

DR. GRADY: Although I would say that I think we are all in favor of more evidence that helps inform judgments, and one of the things that we, I think did specify, was that if there are groups of experts, representative groups thinking about what kinds of findings might

be returned to the specific situation, that they should take into account evidence about the seriousness of the finding, the actionability but also the sort of cost effectiveness of doing something about it, so those kinds of evidence need to be generated.

DR. GUTMANN: So Karen's question does, I think for me is productive of a companion question that just arose in my mind, and I didn't think of earlier when I read this, which is are there subsets of research for which this requirement of dealing with, you know, specifying incidental findings is just another -- is so unlikely that even asking, I mean, is foolish, or do you imagine for those kinds of research you just say incidental findings are not relevant to this research.

In other words, every time you ask for another box to be checked or another line to be written, there ought to be some good evidence based reason for doing that, and we have in mind here research in which there potentially are incidental findings, but there is a lot a research in which there isn't, and is this burdensome to that research or is it just a piece of, you know, it is just a check mark you have to put?

DR. GRADY: I think it could be in some cases just a check mark. So, for example, I'm just dreaming one up now, research with biomed based specimens that are 30 years old and with calcium levels, you are not going to expect that researcher to even if they find an abnormal calcium level to go back and tell the participants that donated their specimen 30 years ago, but at least the researcher has a question in your mind is there anything that I might find that I should do something about, and that is part of the plan.

DR. GUTMANN: Dan and then Barbara.

DR. SULMASY: I was going to turn to one of Christine's additional questions but

I think we are good. The first one about whether there is any responsibility beyond disclosure I think is valuable. Partly we are trying to set some limits I think again on this, reasonable limits.

I certainly don't think that there is a duty that the researcher has to provide the care, as much as many of us would be in favor of having research subject insurance, I am not even sure that this would be covered by that. This is not some harm that was caused by the research itself, it is only something that is uncovered.

The most I might suggest would be at least a moral duty to help facilitate getting appropriate clinical care for the patient, but I think my guess would be that financial burden would lie with the insurance, et cetera, of the individual, and people could perhaps facilitate obtaining the clinical care.

As I am saying this I am also thinking that perhaps these questions of resource poor, that being the US, perhaps in a resource poor environment where the duties might be a little stronger than that, but I think in general there are much more circumscribed to informing and maybe helping to facilitate getting care, but not going to provide the care or underwriting the care.

DR. GRADY: That is why I raised it. I think they are really good questions and I know that I think Betto asked Henry Richardson that question this morning because his theory of ancillary care is you do something about it, you don't just disclose, but that opens up a whole other can of worms, if you will, in terms of what we are suppose to be discussing, but it is also the question what does disclosure entail.

I think we have been envisioning it as giving people information and referring them to appropriate resources, but even that might be more than we are suppose to. I think the question arises should we be offering options of genetic counseling. There are lots of questions

that come with when you give people information what else do you do, and I don't know the answer to that. I am just raising the question.

DR. FARAHANY: We did discuss this, this is a hard issue. So you can imagine we have really difficult views to share, and what you should do with that and whether or not there should be a counselor present or genetic counselor or somebody else present.

Good judgment and input from ethical review consult, something like that should be part of it. But given the myriad of different research contexts which we are imagining and the limitations of knowledge that many of those people we have in facilitating the next steps in care, it seems like even imposing a moral obligation to facilitate a follow up may not be appropriate in many different research settings.

So I think it is a consideration to take into account, which is, you know, to the extent practicable within the knowledge set of the individual to facilitate care that there is a moral obligation given the nature of the relationship that has developed in the research subject to take steps possible to facilitate the next steps, but it may be more like making sure that the person has something like a primary care physician or contact to whom they can turn to be able to help them with the next steps, but it could be limited given the myriad of contexts in which it arises.

DR. GUTMANN: Seems sensible. Barbara.

DR. ATKINSON: I want to go back to the two open questions that were the open questions in the clinical side, because I have very different answers in my head relative to research that I have earlier in the clinical.

The one about if somebody said they don't want to know, you override it. In the research setting I think if it is life threatening I would say you want to try to do that, ask them

again and try to do it, but under any other circumstance I would be very much, this is a research thing, they signed permission for it the way they want it, and unless it is really treatable and life threatening I think that is it.

On the other side of it, if they want to know anything, whether it is minor or not, I don't think they have any -- a research subject who signed a permit that says they aren't going to get anything except what they are going to get that the permit says. You shouldn't give them information, it is a research project, and that is different than the clinical kind of relationship that you have with your own physician.

DR. WAGNER: Do you have any concern, Barbara, about what we have to expect around the competency of the researcher when you do something like that? If you got a psychology project using functional MRI are we imagining the team would have to have someone there that could make a judgment about what is life threatening and actionable?

DR. ATKINSON: I am assuming that the plan would say that, that that would be it. If they would have it or if they've identified it as something like that might be an outcome of that kind of study, they would have something contingency for that. So I am assuming that is how they would pull out what is life threatening, treatable kind of things.

DR. GUTMANN: That is a really good example of why examples are so important. It is not enough to say well, there are researchers who have no competency here, therefore, we don't expect them to do anything, but it is enough to say that as these proposals say, if you are conducting a certain kind of research, say psychological research, which has MRIs then you need, and you have researchers who really aren't competent in this area, you know, of diagnosing, you need a plan that informs the research participants of what they can expect by way of actionable findings.

And there is a wide spectrum of plans that would be ethical, but at the extremes, which is saying we are just not going to look at all because we hire researchers who are totally incompetent first year students, you know, that is unacceptable because that is just too cheap a kind of research to do.

And the other extreme which is we are going to do full clinical scans and follow up with getting them clinical treatment, that is not research anymore, that is already doing clinical work.

So I think having plans within the range of reasonable, taking into account that there is always the good Samaritan exception, and you put that in the plan, if we find something that we can competently diagnose as life threatening, it could happen in this, we will inform and refer the person if they don't have a physician to the best of our knowledge who they should talk to. Something like that can work.

But we do need those kinds of examples like Jim gave so we can see the spectrum that there is of research from the research that is as far away from clinical likelihood of competence in someone to the research that is pretty much interfacing with clinical practice.

DR. ATKINSON: You could perceive in a psychological study finding somebody who is suicidal or depressed or something, too.

DR. GUTMANN: Absolutely. I wasn't trying to suggest that any psychological, but this is on the right track, I think it would be good in these proposals in our discussion of them prior to give some examples to suggest how relevant these proposals are. Yes, Nita.

DR. FARAHANY: I want to follow up on the first thing Barbara raised, which is Christine's open concern, just propose a potential model to see if we can parse, similar to the clinical setting, on whether there is a research difference.

So I think unlike the clinical setting I wouldn't put an ethical obligation on the researcher to refuse a research subject's participation if they decline to have even serious adverse events reported to them.

Although I would say that is an option available to the research plan, which is they could say we will not accept individuals who will not receive it, but they don't have an ethical obligation to do so.

So you have those options if you have given the research subject that option and they have refused to receive even clinically significant results, then I think you shouldn't return the results under those circumstances.

But you could imagine if you are doing functional imaging or some sort of brain imaging where it is more likely that you will end up with something that is a clinically significant, actionable, life threatening kind of condition that you could exclude, and that that would be permissible to exclude research subjects, but if you didn't exclude it then you shouldn't return the research results.

So that is a model that might be one that would parse it in ways that we could agree on.

DR. GUTMANN: I think that parsing is consistent with the reasoning and the parsing we did in the clinical so that is good.

I have three different things, one is to make sure we go down Christine's added list, I am filtering, so we did the one. Dan brought up the one. The two is filtering. What about, is it ethically legitimate to do what might be called the ethical end run, which is anonymize the data to avoid the responsibility? What Christine called filtering.

And I think that just fits into the just say no category, which is that it is just an end run around what the ethical responsibility is, to have a plan, not to put blinders on so you don't need a plan.

DR. SULMASY: Just be careful we don't throw out anonymizing of data. There are good reasons to do that, if that is the sole reason to do it.

DR. GUTMANN: Correct. That is exactly what I was directing it to. When it is -- when the reason to do it, the apparent and actual reason, you wouldn't do it otherwise except to avoid the ethical responsibility, and I think that was the one open one of Christine's.

Now I have Margaret Ryan in neurology. Margaret, where are you? Out in the back. How can we keep a subject's research results from being put in a permanent personal medical record? If a normal healthy control recruit reads the ICF and doesn't want research information placed in an EMR, electronic medical record, clinical electronic medical record through EPIC, which is the one we use, they won't want to participate in research at all. Findings or no, they don't want information in their personal record. Dan.

DR. SULMASY: Yeah, I think it should be possible to do it, whether it is the policy of the institution, it sounds like you are suggesting there are some institutions that make it a policy to put all the research results into the clinical database, I think that would be problematic. There ought to be ways of protecting and producing protective fire walls in those sources of data.

DR. GUTMANN: Margaret, does that answer your question? There should be a policy of not putting research data into personal clinical records? Good. Well, a general policy.

DR. GRADY: If it is clinically relevant.

DR. GUTMANN: That is different. Okay, Judith Brooks from NIH. Judith, where are you?

Should findings that are not actionable in the location where the study is conducted have the option to not disclose the findings to the subject? Can you -- I am not exactly sure.

DR. WAGNER: Research, international research?

DR. GUTMANN: Do you want to just explain?

DR. BROOKS: I think we are talking about research poor settings. So if there is something that is discovered in a research poor setting that is not really actionable and we didn't really expect to have happened and the treatment or care isn't available, would you have an option of not disclosing that sort of information that would otherwise be something that could be treated?

DR. GUTMANN: In another setting? That is a tough one.

DR. WAGNER: What she is saying another category of non actionable for that person.

DR. GUTMANN: It is an ethically different category because it has an injustice component to it. In other words, if this person were in another physical or economic setting it would be actionable.

So this arises most dramatically in how you choose your research settings, right? And what you wouldn't -- well, what you wouldn't want to do is a different kind of ethical end run, which is choose to do your research in a setting where you would be under no ethical obligation to report incidental findings because they are not actionable. The standard of care is so low.

This is not a hypothetical because we actually in other context deal with the ethics of where you do research, and there is a variant on that. Christine.

DR. GRADY: I think this is a really critical thing to put on the table. It seems to me this is why a plan is so important, that there might be times when you are going to do a specific modality, you are going to have a set of findings that you would expect to find using that modality, and you know there is nothing that could be done in that setting. That might be a time when you can't justify doing it in that setting.

I think it just depends on the study and why you are doing it. It seems to me to have, at least in direct answer to your question, Judy, to have a researcher say I am not going to tell them because it is not actionable here, it is the wrong answer, but if there is a plan that says we can find X, Y and Z, but here is what we are going to do about them, which might not include telling every person or might include telling every person, that would be different.

DR. FARAHANY: Just add one to that. It is just that that is part of why that finding was not to say that when the different industry groups provide specific guidance that it not be should or should not return it, it simply provides metrics around the types of findings so that they can be incorporated context specific into a plan.

DR. SULMASY: I was trying to think of an example to fit this, and it might be something like studying cerebral malaria, which you are only going to do in a place where it is common, which would typically be a resource poor area, and lets say you are using some sort of brain imaging that is part of that study and you find a brain tumor, I think what you are going to do with that ought to be part of the plan.

How you are actually going to accomplish that in those settings is a tricky issue.

DR. GUTMANN: I do think that it is an extension of our earlier, the filtering;

which is, if the only reason for doing it in that setting is so you could come up with a plan that you don't have to report those incidental findings, then that is unethical research, that plan should be rejected.

If there are good reasons for doing the research in that setting, and there are a set of incidental findings that in another setting would be actionable but in this setting there is really no reasonable way of making them actionable then a different kind of plan would be potentially ethically legitimate in that setting.

What I just said is a matter of huge controversy as played out in the HIV, doing HIV research, and the one thing everybody agrees on is the only reason for doing the research in a particular setting is to avoid certain ethical responsibilities. That is just unacceptable.

And then there is the larger, separate issue of what obligations you have in resource poor areas for treatments that are hard to impossible to provide in those settings.

I think we have reached the end of our time for this, and Christine wants to say one more thing, and I will gladly give her the microphone because of the wonderful work that she and her group did.

So go ahead, you conclude this portion.

DR. GRADY: Thank you, Amy. I don't want to conclude, I just want to add one sentence to what Nita said earlier.

I agree that there are cases in which it is predictable that there will be serious actionable findings, and if the person doesn't want them they should be advised perhaps not to participate in certain kinds of research, and then there are other kinds of research cases where it would be okay for a person to say I don't want any findings, but I don't want us to say that that is never overridable because I think that there are circumstances that we can't anticipate, and that

participants can't anticipate for which we might want with lots of consultation and stuff like that to override somebody's opting out.

DR. GUTMANN: That is the end of this session, and we will take a break and reconvene at 2:15. Thank you very much.