



Presidential Commission *for the* Study of Bioethical Issues

TRANSCRIPT

Incidental Findings in the Direct-to-Consumer Context

Meeting 13, Session 3  
April 30, 2013  
Washington, DC

DR. GUTMANN: We are going to make a quick transition to our next panel.

DR. WAGNER: Please, Drs. London, Bandettini and Hilgenberg, please come forward.  
I said that wrong! Bandettini. I apologize.

It is my privilege to introduce this next panel to the Commission. This is the first of the panels that Lisa described to us, where we will be able to hear from an ethicist, a practitioner, and someone whose incidental findings were reflected in some unique way.

In this particular panel, we will focus on the research environment, and our first speaker is Dr. Alex John London, Professor of Philosophy and Director of the Center for Ethics and Policy at Carnegie Mellon University.

He's an elected Fellow to Hastings Center and a recipient of the Distinguished Service Award from the American Society for Bioethics and Humanities, and his work has appeared in Science, Lancet, PLOS Medicine, and a Hastings Center report, among others.

He has been commissioned to write papers by the CDC and the Institute of Medicine.

He's a member of the Working Group on the revision of the 2002 CIOMS International Ethical Guidelines in Biomedical Research Involving Human Subjects, and in 2011, he was appointed to the Steering Committee on Forensic Science Programs for the International Commission on Missing Persons.

Since 2007, he has served as a member of the Ethics Working Group of the HIV Prevention Trials Network, and Dr. London's research focuses on foundational issues in research with human participants, issues of social justice in the transnational context, and on methodological issues in theoretical and applied ethics.

Welcome, Dr. London.

### SESSION 3: INCIDENTAL FINDINGS IN RESEARCH

DR. LONDON: Thank you very much, Dr. Wagner. It's a pleasure to be here.

I've been asked to speak about the obligations that researchers owe to study participants

and how these are distinct from the obligations of clinicians to patients, recognizing that this question was asked against the background of incidental findings.

Confusion about the roles and responsibilities of clinicians and researchers has played a critical role in the development of research ethics. Several now infamous cases of research abuse, including the Tuskegee syphilis study, were made possible by the willingness and ability of researchers to use their credentials as care givers to gain access to the bodies of people who were then surreptitiously and unscrupulously conscripted into research.

One of the early goals of research ethics, therefore, was to clearly demarcate research from clinical care, and to require that people only be invited to participate in clinical research after being adequately informed about the activity status as research, about what was required by participation, and about the various and associated risks and benefits.

An ongoing challenge to the informed consent process thus concerns how to ensure that people understand that research participation differs from receiving clinical care.

I want to begin with some important contrast. Research is the social enterprise of generating new knowledge. It serves the legitimate social purpose of supplying the information base necessary to understand human conduct, human health, to create, assess, and improve interventions, and ultimately in the context of medical research, to improve the ability of health systems to understand and to meet the needs of the populations that they serve.

In contrast, clinical care is the social enterprise of bringing to bear current knowledge, expertise and interventions to address the health needs of individual patients.

Each of these is a legitimate social undertaking that promotes distinctive social and individual goods. Insofar as researchers and clinicians are empowered to act in the furtherance of these undertakings and goods, they acquire different privileges and responsibilities.

In particular, the explicit purpose of the clinical relationship is to advance the medical interests of the individual patient. Clinicians have strong fiduciary duties to patients, meaning they have the duty to place the interest of the patient above almost all other competing concerns.

Moreover, they have these duties because they possess distinctive knowledge and expertise that patients lack, which patients must rely on in order to preserve or advance momentous individual interests related to the avoidance of suffering, preserving and promoting their health and longevity.

When clinicians contemplate recommending diagnostic tests or other therapeutic procedures, they must ensure that the risks associated with these tests and procedures are reasonable in light of their impact on the interests of the individual patient on whom they are performed.

In contrast, in order to generate new knowledge, researchers often must subject study participants to diagnostic tests or study related procedures to which those individuals would not be subjected in the context of ordinary clinical care.

Extra biopsies or blood tests required to generate study data are typical examples.

In many instances, the risks associated with these procedures cannot be justified by the prospect that they will advance the health interest of individual recipients.

Rather it is recognized as permissible within clinical research under appropriate conditions to expose participants to risks that are ultimately justified not by the prospect of direct individual benefit but by their contribution to generating important information.

It's also important to recognize that research with human participants is a much broader social activity than is medical care. Some medical research takes place in clinical settings and is deeply entangled with the provision of medical care.

A trial comparing the efficacy of two approved blood pressure medications would be a clear example.

However, a phase one study of the pharmacokinetics of a new drug may involve medical procedures that are carried out by people who are also clinicians. But such studies are often conducted in healthy volunteers and offer no prospect of direct benefit to the participant and are not intended to do so.

Other research is even more remote from the clinical setting, such as neuroscience and

behavioral research, research with human tissue or research with identifiable data. Much of this research is conducted by researchers with Ph.D.'s in fields of basic sciences, computer sciences, social sciences, and even the humanities.

So while some of the individuals who work as researchers also act as clinicians in other context, there are a significant number of researchers who lack the knowledge or the expertise and the credentials to act as a clinician.

Moreover, even when research involves medical equipment, such as imaging devices, these devices are often not used in research in ways that would be adequate for diagnostic purposes in the clinical setting.

Having said all this, I now want to emphasize that the idea that the obligations of medical researchers are exhausted by their duties to advance science has a long and ugly history.

It has been used to justify harm, mistreatment, disrespect, or neglect of research participants on the ground that research advances a greater good.

The traditional reaction to this tendency, I believe, is a misguided effort to appeal to the duties of clinicians as a check or a curb on the very real potential for abuse latent in the idea that research is an essentially utilitarian enterprise.

This appeal to obligations of clinicians is misguided in part because not all researchers are clinicians, and because it diverts attention away from more general values that ought to guide and constrain the researcher/patient relationship.

I have argued that one of the accomplishments of bioethics in general and research ethics in particular has been to bring the institutions of medical research and clinical practice into better conformity with liberal Democratic values of respect for the dignity and equal moral standing of all persons.

These are not specifically role related values. They are values that either apply generally to each person's interaction with other persons or specifically to the way important social institutions have to be structured in order to merit the trust of people understood as free and equal

participants in a system of mutually beneficial social cooperation.

As such, even if we recognize that in order to generate socially valuable knowledge, we have to permit researchers to do things that clinicians should not do. It doesn't follow that this privilege is unbounded.

Rather, if the diverse community members in whose name research is ostensibly carried out are to see it as an avenue through which they can contribute to the common good, then they must have a credible public assurance that they can participate in research without being subject to indifference, neglect, harm or abuse in the process.

To bring this back to incidental findings, I think we have to look at three things. One, the way that specific research activities implicate the interests of participants. Two, the reasonable steps researchers can take to show respect for the interests of participants. Three, how any such requirements would affect the integrity of the research system.

As research becomes more evasive or as it involves activities that are capable of uncovering sensitive information about a person's health or other interests, the participants who make such research possible become vulnerable to neglect and abuse and they depend on researchers to protect their momentous interests.

The features of vulnerability, dependence and asymmetric knowledge and expertise that generally give rise to the clinician's duty of personal care may thus give rise in some specific cases to an analogous duty on the part of the researcher to act in ways that are necessary to protect the interests of study participants.

This may involve a duty to disclose to the participant information that is outside of the study scope, and perhaps link the participant to a professional who can provide appropriate assistance. It may also involve keeping the information, including information that is not disclosed, confidential.

Finally, although I do think there are circumstances in which researchers have a duty to disclose incidental findings to study participants, it is not clear to me that anything I say here would support something like a general obligation to look for such findings.

I have to speak broadly about all kinds of research.

Moving in this direction would have a significant effect on the integrity of the research enterprise. It would divert resources from research to the search for non-research related findings, and it may require training and expertise that many researchers lack.

It may also have unintended effects on prospective participants, some of who may regard the disclosure of such findings as a risk that would serve as a deterrent to research participation.

Thank you. I appreciate your time and attention.

DR. WAGNER: Dr. London, we appreciate those very rich comments.

Our next speaker is Dr. Peter Bandettini. I believe I got it right that time, and I apologize again.

He is the Chief of the Section on Functional Imaging Methods in the Laboratory of Brain and Cognition of the Intramural Research Program at the NIH, National Institutes of Mental Health, NIMH. There, he is also Director of the Functional MRI Core Facility.

Dr. Bandettini has investigated methods to increase the interpretability, resolution and applicability of MRI techniques.

He has been awarded the Scientific Directors Merit Award for his efforts in establishing the NIH FMRI Core Facility, and the Wiley Young Investigator Award at the Annual Organization of Human Brain Mapping meetings.

In 2005, he served as President of the Organization for Human Brain Mapping and is currently Editor-in-Chief of the Journal of Neuroimaging.

His laboratory is currently developing MRI methods to improve the spatial resolution, temporal resolution sensitivity, interpretability and applicability of FMRI.

Welcome, Dr. Bandettini.

DR. BANDETTINI: Thank you. Thanks for having me here. When I prepared this talk, I actually tried to frame the problem as simply as possible. Other introductions have been a little

bit better, but I think what I'm going to try to do is frame the primary issue and just to reemphasize some points that I think are important to me.

First of all, I'm a researcher, not an M.D. I've been doing fMRI research for about 20 years now. I've come across some incidental findings. This is the way I actually look at this issue.

Doing the research, there's about two percent of normal research volunteers who have an incidental finding of clinical significance. It's actually unknown how many truly benefit from follow up on this. Those statistics are not available.

Then the question is what should be done procedurally. Just a little bit of background on what I think are the related issues.

First of all, active brain screening can be expensive and has no clear benefit, at least in the context of neuroimaging over treatment following symptoms. For instance, people could be walking around with tumors all their lives and not have any manifestation of that.

There is obviously other imaging modalities for looking at other parts of the body that are useful. In the context of the brain, it's a little bit less useful.

False positives are a risk, a real risk. They can impact an otherwise normal subject. As was mentioned before, you can obviously affect people's insurance and so on. It's very difficult to necessarily quell those concerns once they have been brought up, even if they are not clinical.

I think this is the most important thing that actually been mentioned in the context of genetics as well, but very different for imaging, and that is most research scans are not clinical grade.

When I collect functional MRI data, so I run a facility where we have 30 PIs. They collect either functional or some anatomical data. The functional scans are incredibly low resolution. The anatomic contrast is very low. Even the anatomic images that are collected with the functional scans are not clinical grade.

For instance, if somebody does report some symptoms, they go into a clinic, they might have a very high resolution scan, and they might have something like a Gadolinium or external contrast agents added where people are specifically looking for something, the question is whether we

should be doing that as well, if we are not looking for something.

The next point along those lines is most researchers are not qualified to read scans for diagnoses, including myself. For instance, when I came across one subject who I thought had an incidental finding, they had very large ventricles and I was concerned that they had very large ventricles.

This is when I was still a graduate student. I showed them the scan. I said oh, this looks really scary. We finally went to a radiologist who then said oh, no, that's within the realm of normal.

What happened was the researcher was alarmed, and I think they still had some residual alarm after that as well.

Those are very real issues that came from somebody who was trying to interpret a scan who wasn't qualified to do that.

Also you have, as I mentioned before, the prevalence of lifelong asymptomatic individuals who might have lesions or tumors. That statistic is unknown as well. We just don't know that.

This is one study. There are two studies right here. I just want to simply show that -- too much information here to really talk about -- basically, the incidents as more and more studies come in is about two percent.

That is pretty much the main figure. It goes up as people increase in age, about 60 or 70 years old, it gets close to eight percent or ten percent. It's about two percent. Both this study and that other study showed that.

And just to emphasize from one of the papers that I referred you to for extra information is researchers who obtain consent from volunteers to provide information about the prevalence of incidental brain findings on brain MRI, the higher prevalence with higher resolution sequences, and the shortage of evidence to inform their management.

I just want to bring out one point here. Really, the harder you look, the more you will

find. It's a continuum. It's not a discrete function.

With our research grade scans, we won't really find much. We're not really looking. If we decide we have an obligation to look more, we will find more. If you do clinical grade scans, you will more likely find even more.

Where do you draw that line in terms of how much effort you put into the quality of your research scans.

This is another quote from one of the papers as well. Brain MRI screening in patients regardless of age, medical history, an example of an ineffective screening program that would produce many inconsequential findings and an exceedingly low rate of clinically relevant findings.

Valuable screening programs must either address a highly prevalent disease or be applied to high risk individuals and must accurately uncover a treatable disease. In other words, here they are basically saying in the context of screening, and I know that's different than doing research and looking for things, but the similarities are, this paper argues, that you really should be looking for something if you're collecting all this multi-dimensional information. Otherwise, you might have more false positives, and you might miss a lot. So it's really not exactly the right place to put this type of effort in the context of research at least.

Once again, this is more detailed than you need to see. I will just summarize it.

There is a whole spectrum of how clinical centers go about handling incidental finding procedures in research. It's wide open. It's still kind of the wild west in some ways. Some clinical centers have scanners that are used not in the clinical setting.

They have a very minimal type of procedure in which no actions are taken beyond articulating a plan for handling incidental findings in the informed consent process.

The unqualified person if they happen to see something, they will refer it to a radiologist potentially. Actually, that's even less than that. They might even say we're not going to even look. If we think we see something, we're not going to tell you.

There is a whole continuum of what people can do all the way up to where I'm at

actually at the NIH. We have an extremely conservative approach. All people doing research scans have to also get a clinical grade scan once a year. We have repeat volunteers. Even the repeat volunteers have to come back every single year, have a clinical grade scan that is read by a radiologist.

The cost overhead of this and the infrastructure is somewhat high. Some people argue about what the actual cost is.

I also think it's a little bit burdensome for the researcher as well, so there are all types of things in between that are once again potentially dangerous, having a radiologist, for instance, try to interpret a research grade scan is difficult. They are going to make more errors, either negative or positive.

Then the question is should there be a standard policy? Should it be a wide open policy? Should it be tailored to specific needs and specific resources of the clinical center or the research center? That is sort of unknown right now.

Lastly, this is from a talk that Judy Illes gave. I'm not going to focus on once again the details. These are the various decision points at which a person could make a decision as to what to do about the incidental finding or how to manage incidental findings.

There are several different decision points where I have question marks that are the unknown's. For instance, how do we actually detect the incidental finding, and who is qualified to read the scans and when, and when they read the scans, who pays for the follow up? Who actually pays for the subject to go to their physician to get follow up scans or follow up research?

Lastly, as I finish up here, the challenge, at least the way I see it, on the one hand we want to catch anything that obviously might be significant to the health of the subject. On the other hand, what exactly would justify the added cost and risk of false positives as well as the fact that the overall effectiveness of screening is unclear.

Therefore, can we even put in this framework of what incidence rate would justify what effort, even an effort of limited effectiveness and clear risks.

With that, I'd like to conclude. Thank you.

DR. WAGNER: Thank you very much. It will be interesting when we get to the full panel roundtable to compare and contrast views on these things.

Our last speaker for the panel has a unique relationship to this topic that we are discussing. Sarah Hilgenberg is a clinical instructor of general pediatrics in the Department of Pediatrics at the Lucile Packard Children's Hospital at Stanford.

She is also the physician lead on Patient Experience, where she works to integrate patient experience and clinical outcomes, and prior to her work at Children's Hospital, Dr. Hilgenberg was a general pediatrics hospitalist at Seattle Children's Hospital, where she completed her residency in general pediatrics.

Of interest to us, special interest to us today, is while she was a medical student at Stanford School of Medicine, Dr. Hilgenberg volunteered for a research study. It was a study involving FMRI, which revealed a potentially lifesaving incidental finding that resulted in neurosurgery.

We are looking forward to hearing your story. Thank you for being here today.

DR. HILGENBERG: Good morning. Thank you so much for inviting me to share my story with you and to contribute to this really important dialogue.

I didn't know this, but that actually was my brain up there on Dr. Bandettini's slides.

[Laughter.]

DR. HILGENBERG: It's okay. To give you a little more context than I had planned, but it's fine. Judy Illes at Stanford as is Gary Glover, whose names were on the bottom of that slide, and this all sort of came together at this time and has taken off in the neuroimaging world, at least. I am one of the people as part of that story.

I'm humbled to be here and I never imagined ever that my experience with my own incidental finding could potentially help others in this way.

At this time of year, 11 years ago, I was preparing to leave on a solo seven week

backpacking adventure to Western Europe. I was a hard working, high achieving, strong willed, Type A, 20 something. I had graduated from a great college with distinction. I had been an All American soccer player.

I was finishing a wonderful two years as a clinical researcher in neurology at Massachusetts General Hospital, and my dreams were continuing to come true.

I had been accepted to Stanford University School of Medicine for admission that Fall.

I was high on life, feeling emotionally, physically and intellectually fulfilled. I looked forward to the challenges and new beginnings that lay ahead.

So it was a few short months later in August 2002, I left Boston where I had grown up in my small tightly packed car for a week long across country trip. Through the side mirrors, I watched everything familiar disappear. I had decided to leave the Northeast, my family, and most of my friends in pursuit of an adventure.

Little did I know this adventure would quickly become more than I ever could have imagined. Not only would I begin to study the art and science of medicine, but I would also learn perhaps the most difficult lesson of all, how to be a patient.

As part of orientation, I spent four days camping in the Sierra Nevada's with six of my new classmates and two second year leaders. Around two weeks after I returned, my camping group received an e-mail from Matt, one of our leaders, who was a graduate student at the time pursuing his Ph.D. in functional MRI. His e-mail said the following "I hope the first week of anatomy wasn't too painful. I had two subjects cancel on me for brain scanning tomorrow morning. Would any of you be interested in having your brain scanned (MRI, not x-ray) while doing a memory test."

Without hesitation, I signed up. It would be \$40 in my pocket and as a new student, I thought great. I was helping a new friend and I thought maybe I would learn something.

So at noon the next day, I reported to the Campus Imaging Center. I signed an informed consent which I didn't remember at the time but looking back on it I found, and I considered only for a moment and then summarily dismissed the possibility of an unexpected finding. Then settled into

the MRI machine.

You have a beautiful brain, Matt related to me after the first of four scans. Of course I do, I had thought.

[Laughter.]

DR. HILGENBERG: After 90 minutes, Matt rescued me from my isolation. Although his barrage of questions from this point on was strange, I answered unphased. No, I had not had any headaches recently. No problem with eye sight nor any other unusual symptoms.

When I asked to see the scans, Matt quickly gathered his materials and ushered me out, explaining that we did not have time. I thought no more of it, and switched my focus to the apple crisp I planned to prepare that evening for a party.

Later that afternoon while I stood at the sink peeling pounds of Granny Smith's, my phone rang. Matt was calling. Voice wavering, he said we found something on your scan. He had seen an abnormality on the third scan of the series and had rushed me out to confirm the finding.

My recollection is that he located one of his mentors, a pediatric neurologist who just happened to be on campus, to whom he showed the images. I have since heard that Matt may have discussed the issue with the Director of the Imaging Center and a radiologist.

Regardless, unsure of a diagnosis because of the non-clinical quality of the scans, they wanted me seen immediately. As you saw in the images, you might imagine why.

In tears, I asked my brand new roommate to drive me to the Stanford University Hospital Emergency Room where I met up with Matt and the neurologist in order to be evaluated.

In a state of utter disbelief, I arrived at the ER. I was ushered into a private room, one I now know to be a place where providers often deliver bad news to families.

There, I waited while an MRI technician was called in from an hour away. While I waited, the Dean of Students, whom I had barely met, visited me in tears, to let me know that I had the School's support. A touching but terrifying gesture.

I learned later that those initially involved had thought I had a brain tumor. I phoned

my mother in Boston, trying to explain while sobbing what had happened without knowing the details. Unable to reach my father and stepmother, both physicians in New York, I continued to try until I succeeded with one of those awful phone calls that every parent dreads, waking them out of sleep to tell them something was terribly wrong.

Ultimately, that Saturday afternoon into evening, I was evaluated by an ER physician in the Neurosurgical Service, and I underwent a diagnostic MRI, and then was brought into a small dark room to look at the images and to receive the diagnosis from the pediatric neurologist who had accompanied me earlier that day.

Sarah, what you have is an AVM. Do you know what this is? It stands for arteriovenous malformation. Have you heard of the Circle of Willis? Although I would come to love the Circle of Willis, at the time he spoke a foreign language, and the rest of what he told me is a blur.

I do not know whose choice this was but I ended up being admitted to the hospital that night through the following morning for "psychosocial reasons," I was told. I stayed up the entire night alone and terrified and was discharged the following morning in a continued state of shock.

I went to class for a few days, telling only a few classmates what had transpired. My parents flew out just in time for my white coat ceremony, and then an appointment with the Chief of Neurosurgery at Stanford, who happened to specialize in AVMs.

My parents then left and I stayed in California to continue to attend class. Agonizing over what I should do but feeling the need to stay occupied.

The following week, I had an angiogram. On the basis of the results, my physicians recommended that I undergo two embolizations and a resection. Knowing that the AVM could bleed, I chose not to postpone treatment for too long and scheduled the procedures like any good student for Thanksgiving and Christmas breaks.

In the meantime, I elected to stay in medical school, and as you can probably imagine, life as a student proved very difficult. I was learning firsthand the material taught in class, the vulnerability of the body, and in particular, of my brain, the organ ultimately responsible for getting

me into Stanford.

I underwent my first embolization after classes finished but before finals began. I lay in bed for about 48 hours afterward with a truly debilitating headache. It was difficult for me to walk for a few days afterwards because of soreness in my groin where they had accessed my femoral artery.

I took my finals early, then had a second embolization, and ultimately a definitive resection.

Although longer than anticipated, the surgery went well, and following a post-procedural angiogram, my neurosurgeon delivered the news, I was cured. He was pleased to have resected the 3.5 centimeter frontal AVM because he thought it most likely would have caused a devastating bleed.

The physical recovery of the surgery was remarkably not as difficult as the emotional recovery. I struggled with post-surgical depression, which I have since learned is relatively common.

I decided to take an extra year of medical school so as to spread out my course work in order to find a balance with extracurricular activities, including research, teaching and athletics.

I spent a lot of energy trying to make sense of all that had happened.

Three months after my surgery, I met with my neurosurgeon and was officially discharged from his clinic because he no longer needed to follow me.

I have had no adverse health sequelae. I believe I've had the best outcome I probably could have had.

A few years after my surgery, I met my husband, who happens to be a pediatric cardiology fellow, who performs genetic research on congenital heart disease, so this is also a part of our daily lives.

I graduated Medical School to complete a pediatric residency at Seattle Children's Hospital and University of Washington.

I have a promising and fulfilling professional life as a pediatric hospitalist at a major

academic center, enjoying both the privilege to help patients and families work through their illnesses, and occasionally during incidental findings, and to help shape the future of medicine by teaching residents and medical students.

In 2011, my husband and I had a daughter, Hannah, who is the most special person in our lives. I was so unbelievably thankful that I no longer had an AVM in my brain during childbirth as I learned this is a common time for one to bleed.

While I am just one research subject whom none of you had met prior to today, I am a really important person in a few other people's lives.

I am grateful that Matt decided to tell his superiors about my scan. A part of me thinks he had no obligation to do this. I am not sure I would be here today to speak to you if he had not acted.

I do think it is important to try to have a plan in place to address these issues as they arise.

Thank you again so much for inviting me to be here with you today.

DR. WAGNER: You are most welcome. Thank you for coming and adding powerfully to three different perspectives on the issue of incidental findings related to research.

Colleagues, who wants to begin questioning? John? Raju? Christine and Dan, by the way, you guys have a pass if you want to begin.

DR. SULMASY: I'll use mine at the panel.

DR. ARRAS: Thanks for a really interesting panel. Alex, I am puzzling over the obligation to inform patients of incidental findings or come to their aid in some way.

If we switch from a standard fiduciary model of the physician/patient relationship to your model, which as I take it is based on sort of liberal Democratic principles of equal respect and equality, when we are dwelling in the fiduciary model, it's fairly direct and clear what impels a care giver to provide that assistance in the presence of a really dramatic incidental finding.

He or she is my patient. They're vulnerable. I have more knowledge, more power. I

have an obligation to come to their assistance.

I need some help in flushing out your account of how it is that a non-fiduciary model would get us to roughly a similar result in a lot of these cases.

It seems to me that the standard liberal political theory values tend to be sort of framed in negative terminologies, you know, respect the autonomy of the individual and so on.

What is it within your integrative model that provides the impetus to assist as opposed to anybody else in the community who just is passing by and just happens to know something?

DR. LONDON: Thanks. What I would say is that there is not a cookie cutter in the sense of when you have the underlying fiduciary duty, then you have broad-based justification.

When it's lacking, then you have a variety of different kinds of encounters of different depths, different significance, over different times, different degrees of vulnerability that are arising, so what I would look to, you look at the factors that underwrite when it is that you had a fiduciary duty.

When there is asymmetric knowledge, when there is vulnerability, when the person has -- if you go back to Henry's model and the person has made themselves vulnerable or entrusted a particular part of their care to someone, then I think the relevant question then is how do we -- understanding that a researcher's job is to generate data, ask questions, answer very specific questions, how do we reconcile that with the need to treat study participants as more than just data points in this.

They are real people with whom you are engaging and you are learning private information about them. If that private information is clearly significant for their health, then I think there you would say you have sort of a duty grounded in beneficence and the special access you have to this person's body to respond to them in a way that shows respect for their interest.

I think that becomes muddier as you add uncertainty. I think Dr. Hilgenberg's narrative was really important and nice because there was a lot of discussion of the anxiety she went through before this was confirmed, so you can imagine the case where Matt is wrong, and they come in and

they say, you know, it turns out it wasn't anything, but there was still all the distress with everything that had happened.

I think that is why without the umbrella of a general duty, you have to make more nuance decisions that factor in, how reliable is this information, and the features of vulnerability that we mentioned.

DR. WAGNER: Amy?

DR. GUTMANN: I just have something that I think just needs to be said. Dr. Hilgenberg's story is one that I think every human being can relate to in a way that doesn't decide the many difficult issues we have, but it does speak to something that Dr. London and Dr. Green and Dr. Cho and Dr. Cowan, a lot of people have either specifically said or alluded to, which is there is a kind of minimal standard of what human beings who have a basic ethical sensibility will say to themselves, if I don't do this, I can't sleep at night.

There are some incidental findings, take the clinical setting away, because there, there is a fiduciary duty, but in research or I would say we should question in direct to consumer, where something jumps out at you that is so possibly threatening to somebody's health and well being, that it's a minimal human duty to do something.

Now, not to do something foolish, not to do something rash. To do something with caring and finding the people who have the expertise to help.

It seems to me we owe it as a Commission to take a story that is a true story and basically recognized that sometimes you may not have a legal obligation, it's even a question of whether there's a duty, but not to do something would be so obviously wrong.

I don't think you have to be a liberal Democrat or a conservative or any other thing to recognize this. I just wanted to say there are some things that when you find out about them and they affect a human being and possibly could save their lives, it's the right thing to do.

DR. HILGENBERG: If I could reply just really quickly. Thank you so much for saying that. When I was speaking to my husband after this invitation about what I wanted to say, I

wanted to say just that at the end of my comments, but felt it needed context. I really appreciate that.

DR. KUCHERLAPATI: Thank you. I have a question for Alex London. If I understood correctly, there were two points you were trying to make. One of them is research results should not be reported back to the individuals, and I think we heard comments from both Sarah and from our Chair about circumstances when that would be appropriate.

The other point that you made also is that revealing such information might actually prevent an individual from participating in research studies.

I just wanted to get your opinion on this, which is completely different. There are some people who believe that as the name indicates, people who participate in research studies are called "human subjects," they're subjects.

That notion that they are subjects and not real partners in research is actually hindering the ability to be able to bring people into research.

Many people, what drives their motivation for participating in studies is not only to provide information for society, but also to obtain information about themselves.

How do we reconcile this view and what do you think about the view of changing the way we think about this, individuals who contribute to research studies should not be considered as subjects but as partners in that endeavor?

DR. LONDON: Thank you for that question. Yes, I agree with the last thing you said. I'd like to go back to a point that was made in the first presentation. People participate in research for diverse motives. That is researchers, participants, people who fund it.

It is not necessarily everybody is out solely to improve the standard of care. People want to make money, they want to get access to health care, they want all these other things.

That is not something you can change. The goal of this sort of system level view that I am encouraging you to take is to say look, how do we design a system that can manage those diverse motives so that all the relevant stakeholders can be confident that even though people participate in this for diverse motives, it is still going to do the thing that we want it to do, namely generate valuable

science.

I think that's the tension here in research. You want research to generate information. It's a valuable social activity.

There are scarce resources to do it, mostly because of the funding decisions people make. The more you divert resources away from that, then the less science you are going to have.

Having said that, I think there is this constraint that the people who participate in research, you want them to participate as a partner, you want them to have buy in to I think this is important, that's why I want to contribute to it. They also want to get these other things, but my participation should contribute to something.

I think there are cases in which you say look, we have to deviate some resources here to help you because you are a person -- I don't think there is a general duty in research to say now that I have you as a research participant, as a benefit, I'd like to droll through a whole bunch of things to see if there is something I can give you. I don't think that is an appropriate model.

The other thing you asked about was some people might be discouraged to participate. I don't have a specific case in mind. I can imagine someone would say look, there is a chance that I would have a susceptibility to something like Alzheimer's Disease or something like this, and I'd like to be able to contribute to your study without knowing about that, I wouldn't want to know about that. I'm happy not to contribute to your study but if there was a way I could do it without learning about that, I would do it.

That doesn't seem to me like a crazy attitude or one we should disregard. I actually think that's an attitude that would potentially help advance the science because it says look, maybe there are certain things that we can wall off or compartmentalize, and where there may be things where participants also want those things to be compartmentalized.

DR. GRADY: I agree. I like the way Amy framed the idea that when something hits us in the face, we need to do something about it. I think probably everyone has that instinct.

I think it raises for me some very interesting questions, two ends of the question, and all

of your comments have helped me think about this.

One is how confident do we have to be that we're seeing something. This is Dr. Bandettini's data. We have research scans and researchers that don't read scans. Something looks like something to some people and doesn't to other people, I guess is the way I would say it.

How do you make a policy about what do you do. That is one thing.

The second side of that is yes, we all have this instinct to do something. What do we do? What is sufficient to do? What is required to do?

The first thing, of course, is telling you, right. In the story you experienced, Dr. Hilgenberg, you had Stanford Medical School at your disposal. So many people, especially in the research context, don't.

If we just tell them you have something on your scan and you need to go follow up, what's our obligation as researchers, I guess, how far does it go? Do we have to find them the next level of scan? Do we have to do the clinical scans every year? Do we have to refer? Do we have to pay for the care?

There are so many questions that follow on that are not easily answered, but I think are part of what we have to struggle with in terms of what does it mean to have an obligation to do something.

The last thing I want to say, and this gets back to the earlier panel, Lisa set up research clinical care and direct to consumer. I think the context is very important in terms of how these questions get answered.

I want to highlight that Mildred added a fourth context to that, that we didn't think about, and that's public health. Public health has some really different implications in terms of using whole genome sequencing for screening everybody, and what does that mean in terms of what the minimum results are that we need to return and to whom.

Those are other questions I guess we need to talk about, but it doesn't require anybody to answer.

DR. WAGNER: It is an important discussion for the Commission. Do any of you want to comment?

DR. BANDETTINI: I think that is the framework. I think nobody disagrees that when something jumps out, you should do something. That is exactly right. Something will jump out more in certain scans than other scans, and then the really difficult question is you can keep on looking but it's a slippery slope. You can devote all kinds of resources and then where do you stop. Should that be context dependent in some sense.

DR. GUTMANN: It's not a slippery slope, that is it doesn't have to be a slippery slope. It's only a slippery slope if you can't make any distinctions between what is subject to expert interpretation, what has some clear potential for helping a person.

I would just say there are many difficult issues here. I just want to correct, because if you say it's a slippery slope, it tells you don't start down here because you are going to slide all the way to impossibility.

It isn't. That's why I began the way I did. There are some things that even a pretty inexperienced researcher, if it jumps out at her, let's say, and she's in an academic medical context where she has a Dr. Hauser who she can in confidence say can you take a look at this and tell me whether I should be concerned because I am, and you have more experience than I do, which is actually true in this case, what would you suggest the next step be.

I just would like us not to avoid going to what is the ethically obvious fundamental, just because there will be some lines we have to draw, so it doesn't become a slippery slope.

DR. WAGNER: Are you going to comment on that?

DR. HAUSER: It was just an observation, Peter, as you were speaking, and with Chris' comments. We do have some level of comfort and I think appropriately so in clinical medicine, particularly with neuroimaging, to limit the scope of investigation, and in part because of the time constraints in a single study, for particular clinical implications.

For example, we will often look at certain systems, hearing or vision, or spinal cord, of

course, without visualizing with a clinical scan the entire nervous system.

In those settings, we would miss a lesion that was in a non-visualized area.

DR. ALLEN: I want to continue what I regard as the justice issues that Christine Grady was raising. It began to occur to me listening to your story, Dr. Hilgenberg, because you emphasized it was a new friend that you agreed to work with with the brain scan and this new friend found the suspicious lesion, the new friend then acted on it in a way which probably saved your life.

A lot of us don't have friends, and this Commission has looked at some pretty shocking and outrageous and scary examples of researchers who did not treat their subjects well. You were lucky.

I guess what I want to put on the table for the Commission is the question of how do we think about the fact that some subjects will be like you, a super star, that everyone wants to befriend and help?

If you walk in for a scan or Barack Obama walks in for a scan, everyone is going to be solicitous to their needs.

If Joe or Jane Average walks in and Joe or Jane Average is uninsured and maybe needs the \$40 to buy diapers and hamburger meat, and has no capacity to pay for surgery if it's needed to cure an incidental finding condition that's discovered, what do we do about that?

Alex, you raised the question of who pays. I'm very concerned that in the context of research we don't unfairly neglect the needs of subjects who don't have resources and who we don't like and who are not our friends.

Also, I just want to emphasize how important it is, if we are going to have a sense of a minimal standard, the kind of you can't sleep at night because you didn't pursue it, don't we have to also have some kind of financial medical infrastructure that ensures people who are research subjects are going to get taken care of if it turns out they have an unforeseen condition.

I just wanted to know what the panel thought. Alex, I think you agree with me that something needs to be there structurally. I am wondering whether the other panelists agree as well.

DR. BANDETTINI: Actually, I completely agree. I think that within our infrastructure we should do as much as possible, and then the question is what is reasonable, what is as much as possible.

Like at the NIH, we have this clinical grade sort of scanning and we have a radiologist interpreting every single one. Is that overkill? I don't know. NIH can afford that. Other places maybe can't.

DR. HILGENBERG: I guess I'll just say in my professional life, I'm a clinician, you don't turn people away at the door who don't have insurance and so forth. I'm not sure how to address if things are discovered in research, you need to treat that differently. Obviously, that's why we are here and discussing this.

Clinically speaking, I think that person could show up at the door and say I had this, somebody found this and I'm concerned about it, and it would be hard for me to imagine they would be turned away despite them not having insurance.

DR. ALLEN: We have a system now which hopefully everybody will have some kind of insurance very, very shortly. I'm not convinced that the researcher who finds something will necessarily treat -- respond the same way to the finding.

We have a question of do we respond in an equitable way to similar evidence of a problem and then will the person who is eventually told have the resources, financial, moral, social, otherwise, to deal appropriately with what is found, and how can we ensure that will help that process results in an optimal health solution.

DR. WAGNER: We will have an opportunity to follow up on all this with this panel and the prior panel at the roundtable session scheduled, but I think we need a brief break at this point, but not before thanking the three of you.

(Brief recess.)