



Presidential Commission *for the* Study of Bioethical Issues

TRANSCRIPT

Incidental Findings in the Direct-to-Consumer Context

Meeting 13, Opening Remarks and Session 1

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Washington, DC

WELCOME AND OPENING REMARKS

DR. GUTMANN: Good morning, everyone. I am Amy Gutmann. I'm president of the University of Pennsylvania and chair of the Presidential Commission for the Study of Bioethical Issues. And on behalf of myself and my vice chair, Jim Wagner, I welcome you all to this, our 13th meeting. Before we continue, I want to note the presence of our designated federal official, Commission Executive Director Lisa Lee. Lisa, could you please stand? Great.

Before we begin our deliberations today, I just want to thank two of our former commission members who have retired from the commission. I think it's appropriate to formally thank them. Lonnie Ali is a tireless and outspoken advocate working to raise awareness of Parkinson's Disease as well as increase funding for research. While on the commission, Lonnie consistently brought her well-reasoned and compassionate perspective to bear during our deliberations and our reports.

Dr. Alex Garza is the former Assistant Secretary for Health Affairs and Chief Medical Officer for the Department of Homeland Security, and he brought unique insights to all of the Commission's topics as an emergency physician and as a public health expert. I know I speak for everybody on the commission when I say that we are extremely grateful for their service and we will miss them.

We look forward to what we expect will be equally impressive future

endeavors and the White House is working to appoint two new Commission members. But until we do, we can work as a full complement of a Commission. So -- but that means everybody on this Commission now has a little bit more work to do.

So at this meeting, we are going to turn our full attention to our next topic, which we expect we'll issue in a report, and that is the topic of incidental findings. We discussed this at the close of our last meeting. The Commission's next report will be devoted to the distinct ethical issues raised by incidental findings in three contexts: clinical care, research, and commercial direct-to-consumer testing.

Emerging medical technologies, changing cost structures, and evolving medical practice have made the likelihood of discovering incidental findings in different contexts a certainty. The Commission, therefore, will begin our incidental findings project at this meeting by delving deeply into related ethical and empirical dimensions. It's not a new topic for this Commission. We hosted speakers on incidental findings at both meeting 4 and meeting 10, and we've heard from experts in the field such as Susan Wolf and Bartha Knoppers, who gave us their views on the ethical frameworks that should guide incidental findings.

The Commission began its engagement with this topic in a report that we issued entitled *Privacy and Progress in Whole Genome Sequencing*. We released that in October 2012. We made several recommendations relevant to

incidental findings. We recommended that informed consent forms for whole genome sequencing research should include what data and information, if any, might be returned to the individual.

We also recommended that individuals be made aware that incidental findings are likely to be discovered in the course of whole genome sequencing, and that the consent process should convey whether these findings will be communicated, what the scope of the findings are, and to whom the findings will be communicated.

And finally, we recommended that funders of whole genome sequencing research should support studies to evaluate proposed frameworks for offering return of incidental findings, and to investigate the related preferences and expectations of individuals contributing samples and data to genomic research and undergoing whole genome sequencing in clinical care, research, or commercial contexts.

So why are we doing a separate report, having already recommended -- made these recommendations? Because we are so impressed by the richness and the ripeness of this topic for ethical review that we thought, in addition to our recommendations in whole genome sequencing, we really needed to delve deeper and more broadly into all the realms in which incidental findings occur. Whole genome sequencing is truly only one of a broad spectrum of realms where incidental findings are extremely likely.

And whole genome sequencing -- if all one does is get one's whole

genome sequenced, it's certain that there are going to be incidental findings. And so we began there. But far more common are some of these other contexts.

So this new report will consider incidental findings not only resulting from genetic testing, of which whole genome sequencing is a subset, but also from other modalities such as imaging, biological specimen testing, and in the contexts, as I said earlier, of research, clinical care, and direct-to-consumer offerings.

So before we start off this meeting, I'd like to take a moment to explain how we'll take comments from the audience, which we welcome. There is at the registration table cards, and there also -- every staff member has some cards. Would the staff members please stand up? And so if anyone wants to make a comment or ask a question, just get a card, fill it out, hand it to any staff member. And staff members are all wearing badges like this. And they'll get them up to either Jim or myself.

And time permitting -- and we almost always find some time to bring the questions and comments -- we will read them aloud and ask Commission if -- any Commission members who would like to respond. And with that, we're ready to go. But Jim, let me turn it over to you.

DR. WAGNER: Oh. You have, as usual, summed the problem very well. Amy, I will tell you, I -- as reading the background materials and re-visiting what we did around genome sequencing, my mind keeps going back to our fundamental principles. Sort of the three Belmont and then the two that we added. But specifically, the way we have incorporated respect for persons into our

stewardship principle.

DR. WAGNER: And for me, this incidental findings question seems to add a new dimension to the stewardship question. It's a problem not so much -- the stewardship is a problem not so much about how those unable to represent themselves concerning potential but knowable risks, which is how we usually apply stewardship, but rather, it applies to a group of patients or subjects or consumers who may be fully able to represent themselves but who find themselves in a situation without the ability, a priori, to know of the risks that could be discovered.

So the questions posed by incidental findings may challenge us, it seems to me, to address possible conflicts arising in the exercise of some of our existing principles, perhaps even challenge us to pose some new ethical guidelines for the obligations of physicians and researchers and providers toward patients and subjects and consumers, in order to perform the service, the clinical diagnosis, the research, whatever it is, in such a way that still treats the wishes of such patients and subjects and consumers with compassion and respect.

I don't know of a group I'd rather be taking on this challenge with, our chair and each of you, so welcome to a new session.

DR. GUTMANN: I would like to do two things to get us started. First is to begin with Nelson Michael and go around and have each Commission member introduce himself or herself.

DR. MICHAEL: I'm Nelson Michael. I'm an HIV researcher at the

Walter Reed Army Institute of Research.

DR. ALLEN: Good morning. I'm Anita Allen. I'm professor of law and philosophy at the University of Pennsylvania in Philadelphia.

DR. ARRAS: I'm John Arras. I'm a professor of philosophy and public health ethics at the University of Virginia.

DR. FARAHANY: I'm Nita Farahany. I'm a professor of law and philosophy and a professor of genome sciences and policy at Duke University.

DR. HAUSER: I'm Stephen Hauser. I'm professor and chairman of the Department of Neurology at the University of California, San Francisco.

DR. ATKINSON: Barbara Atkinson. Emeritus Executive Vice Chancellor at University of Kansas Medical Center.

DR. KUCHERLAPATI: I'm Raju Kucherlapati at Department of Genetics and Medicine at Harvard Medical School.

DR. GRADY: I'm Christine Grady at the Department of Bioethics at the NIH Clinical Center here in Bethesda, Maryland.

DR. SULMASY: Dan Sulmasy, the Department of Medicine and Divinity School at the University of Chicago.

DR. GUTMANN: Great. And the second thing I'd like to do is invite our executive director, Lisa Lee, up here to the table to give us a brief overview of the landscape in the ethics of incidental findings. Lisa, so you could kick us off in that way. Welcome.

SESSION 1: OVERVIEW OF INCIDENTAL FINDINGS

DR. LEE: I'm happy to be here. Good morning all. As Dr. Gutmann mentioned, we -- the Commission started considering this issue of incidental findings over two years ago, when we first started our work on whole genome sequencing. Can I have a clicker? Thank you. Thank you.

I'm going to just go over quickly the scope, modalities, and the context of incidental findings. All of this overview will be fleshed out during the meeting today. I'm going to start with scope. And I'm going to talk a little bit -- in Privacy and Progress, we defined incidental findings as information gleaned from whole genome sequencing, research, or clinical practice that was not intended or

the expected object. There's debate in the literature about the definition and the importance of clinical significance, reproductive significance, misattributed paternity, or parenthood.

So we're going to start with this working definition of information gathered in the clinical, research, or direct to consumer setting that was not the intended aim of the test. And we will talk about this in the context of potential clinical, reproductive, or health significance.

Now, some really dislike this term, incidental findings, and have suggested other terms entirely, like serendipitous or iatrogenic findings, or non-incidental secondary findings, unanticipated findings. Whole bunch of different synonyms. But for now we'll stick with this.

Broadly, though, there are practical, legal, and ethical considerations here. In terms of returning results, it's unclear whether all persons who have these results have the necessary expertise to understand appropriately and convey the necessary information to people receiving these results, raising concerns around professional ethics and our expectations of persons giving these results.

Practical considerations around managing and interpreting and taking into account individuals recipient preferences, also an issue, raising issues related to autonomy and beneficence.

Legal considerations, any test results that can be returned must be conducted or -- in a CLIA, certified laboratory. And this might not be the case, particularly for tests conducted in a research setting.

In addition, if incidental findings are discovered, there may be issues associated with the health care provider choosing not to return them yet, being concerned about legal liability in the case of future potentially preventable damages. Then being concerned about avoiding this potential liability and health care providers might conduct, then, more tests and additional things that would result in potentially more incidental findings. So this idea of defensive medicine.

The ethical considerations -- this project really presents us with an opportunity for timely deliberation of how ethical principles give rise to particular duties. The duty to look, the duty to warn, the duty to rescue, the scope and stringency of which might vary depending on each of these particular contexts.

On this topic, we'll hear this morning from Dr. Ruth Schwartz Cowan, who will provide us the broad perspective on things that should be considered in assessing these emerging technologies. Dr. Robert Green has thought a lot about incidental findings in his scholarship and in his leadership in the American College of Medical Genetics and Genomics, and he'll talk with us about recommendations of returning genetic incidental findings in the clinic.

And Dr. Mildred Cho, who will provide us with deeper understanding of current issues associated with incidental findings, broadly, and a sense of which issues associated with us are still unsettled.

We're going to talk a little bit now about modalities. The three listed here we discussed. With genetics and genomics, obviously we're going to talk here about the whole genome sequencing, whole exome sequencing, other large

scale testing. Not about discrete testing that gives us an answer for a single test without additional information. But these large scale testing.

The types of incidental findings? Some are known, like a predisposition to Alzheimer's or BRCA, et cetera, the breast cancer gene. But an individual will have thousands -- hundreds of thousands of variants that we don't know what they mean yet. And that's an incidental finding that, as Dr. Wagner suggested, is a whole different set of circumstances.

Specifically, in terms of considerations that apply just to genomic incidental findings, there usually aren't additional tests that need to be done to shed more light on the findings, but it does lead to potential additional preventative measures like -- for the example of BRCA, it might lead to something like a preventative bilateral mastectomy. Pretty substantial intervention. Or additional screening procedures like routine mammograms. So the implications can be enormous.

Most findings are predictive about propensities. They are not -- they can't predict with certainty, so there are those issues too, specific to genomics. And finally, there might be implications for relatives who might or might not have consented for any of this information.

For imaging, -- so this includes scans, X-rays, ultrasounds, other imaging -- incidental findings of scans of the abdomen and pelvis might include things like liver, kidney, adrenal glands, et cetera, and they're likely to reveal masses that might indicate cause for concern.

Specifically to imaging incidental findings, some percentage of these masses are benign. A much smaller percentage of these are likely to be something harmful. CT angiography, for example, which is a technique that evaluates the heart using imaging -- over 50 percent have some kind of finding. At least one non-calcified nodule. Less than 1 percent of these are of concern -- are malignant. That means 99 percent of these are benign.

But follow up can produce lots of anxiety, be costly. They have high morbidity risks, and further investigation can generate additional incidental findings.

For biological samples -- we're talking here about blood, urine, et cetera -- this, in terms of types of incidental findings, you do a chemistry screen. That's a panel of 14 tests that is just a broad kind of screening. Includes kidney function, liver function, electrolyte and fluid balance. The test is intended to look for appropriate levels in one area and reveals abnormal levels in another.

Healthcare providers are trained, generally, to only test for what they're looking for and to not do other tests. But only those that will change patient management. Careful consideration, therefore, is given to whether they should order a renal panel, for example, with seven measurements versus one with twenty measurements. So healthcare providers are well-trained in this. But once abnormal findings are found, it's really difficult to ignore them.

Specific considerations to biological incidental findings is that a healthcare provider can anticipate a finite set of incidental findings with these

kinds of tests. It's not like genomic sequencing where who knows what you're going to find. It's pretty controlled in this setting.

All right. Let's talk a little bit about contexts. So in the clinical context, incidental findings arise when a healthcare provider conducts a test with the goal of diagnosing one thing and finds something else. The ethical considerations here are that the healthcare provider -- oh, we're all very familiar with this -- the fiduciary duties to patients. and I say healthcare providers, I'm not talking specifically physicians. I really mean this in the broadest sense, including physicians, nurses, laboratory technicians, genetic counselors.

And it really involves here reconciling beneficence and non-maleficence. It's not always clear that returning incidental findings will provide more benefit than harm, and it's really that, that we need to think about. How the duties to look, the duty to warn, the duty to rescue actually apply in this setting.

There are laws that govern the return of incidental finding, and the healthcare provider's duty. The legal duty to warn or to return incidental findings exist. And again, the concerns about the defensive medicine is a concern. Additionally, reimbursement is a potential practical consideration. It's not clear that insurance will always reimburse for this. And additionally, some insurance claims might lead to incidental findings being treated as pre-existing conditions. So there's that concern.

So overall, healthcare providers are generally thought to owe a

fiduciary duty. It raises the question of when returning incidental findings is in the best interest of patients. So on this topic today, we'll hear from Dr. Haavi Morreim, who's a philosopher and a lawyer, and will speak on fiduciary duties owed to healthcare providers. And the way in which obligations that healthcare providers have is distinct from the duties that researchers have to participants.

Dr. Danielle Ofri will share her experiences as a healthcare provider and her experiences dealing with incidental findings. And finally, we have Ms. Carol Krucoff, who will share her story as a recipient of incidental findings in a clinical setting.

The research context. Here we have a variety of research protocols that give rise to a variety of research-participant relationships. These protocols have the potential to give rise to a variety of incidental findings, as you might imagine. So the ethical considerations here are things like the potential incidental findings and the constraints of the researcher's ability to return these findings. Both in terms of their expertise and in terms of the obligations they owe the research participants.

What do they owe them? Is a partial entrustment model informative? Again, we're considering the duties to look, to warn, and to rescue in this relationship. Again, there are legal considerations. We talked earlier about the implications of CLIA, that laboratory tests and such must be done in a CLIA certified laboratory in order to be returned. If the data are de-identified, re-identifying them might not be appropriate, possible, or legally permissible.

There is a small possibility or concern about legal liability for researchers returning incidental findings, but this is currently unlikely. So there's varying degree of skill and expertise among researchers to both detect, interpret, and communicate findings. Research-grade imaging is often insufficient for clinical interpretation. Big practical concern here. Researchers also have limited budgets, and to expend the money on -- in the pursuit of generalizable knowledge, which is what they're doing, versus whether they should return incidental findings or spend the money in that arena.

And then of course the question of what is appropriate for an IRB. So there are a number of models and approaches that have been used for returning incidental findings to research participants. And they consider a variety of factors, including how practical it is to return the results, whether the results -- the findings are actionable, et cetera.

To address this question today, we're going to talk -- a couple of folks are going to talk with us. Dr. Alex John London, who is a philosopher, will talk with us about setting forth the obligations that researchers owe to participants and the ways in which the ethical obligations are distinct from healthcare providers.

Dr. Peter Bandettini will talk with us about his research and neuroimaging expertise, and Dr. Sarah Hilgenberg is a recipient and she will talk with us about finding an incidental finding and her participation in a neuroimaging study. And she credits this incidental finding with saving her life.

Finally, in the direct-to-consumer context, here we have this interesting intersection of medical ethics and business ethics. This is a relatively recent emergence, so we have this ethical terrain that is the least explored. All of the modalities are offered here in the direct-to-consumer context, so we have all of the ethical considerations from the three different modalities.

Given the scope of what will be returned -- given that that's generally set forth in the contract at the outset of the procedure, there are questions about how and when, or even if direct-to-consumer testing can give rise to incidental findings. So we have the ethical considerations of ethical principles of business ethics. What obligations do direct-to-consumer companies have to consumers to return results if it says something clear in the contract that's different? What models or theories can be useful in this case? Stakeholder theory, integrative social contract theory?

And then how do our traditional medical ethical principles apply? Beneficence, respect for persons? Should people who are interested consumers be involved in decision making processes? Should we open up a democratic deliberation for this? There have been ethical problems documented with previous investigations with direct-to-consumer genetic testing, and how do these problems intersect with incidental findings, should they be considered? And again, how do the duties to look, warn, and rescue apply here?

Legal considerations exist. Practical considerations exist. We'll have three speakers today on this topic. Dr. Thomas Donaldson will provide us an

overview of social contract theory and an account of when companies owe obligations to individuals beyond that set forth in the contract.

Ms. Gail Javitt will talk with us about some of the parameters of incidental findings in the direct to consumer context, including the contractual relationship between the company and the individual consumer. And Dr. Joanna Mountain from 23andMe will provide us with a perspective about how one leading direct-to-consumer genetic testing company thinks about handling incidental findings.

So we've covered all three of the main areas here and I really look forward to today's discussion, both our speakers as well as the panel's deliberation. Thanks.

DR. GUTMANN: Thank you very much. That was really an excellent overview of mapping the terrain of incidental findings and also, not coincidentally, mapping the terrain that we're going to cover today with our wonderful group of speakers. Any questions from Commission members to Lisa before we move on? I would just say that where you began, which is with a very -- a clear definition which doesn't beg the question is, I believe, the right place to begin. People -- a lot of people or some people want to define it so as to basically bias the conclusion one way or another. In other words, to narrow the notion -- the very definition of incidental findings so it leads you one way or another.

Whereas the definition that we used in whole genome sequencing

and the one you presented is -- it doesn't beg any question. It's a broad definition which allows you to look at all the different ways in which incidental findings arise, and then we can use empirical and ethical considerations to reach conclusions, rather than have the definition itself lead you to a conclusion.

It basically says, an incidental finding is something – in whichever modality you're using -- it's not what you're looking for. It's something you find that you weren't looking for. And then it just opens up the question, what should you do with it?

Good? We're ready to move on.