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TRANSCRIPT

Bartha Knoppers, Ph.D.

Director, Centre of Genomics and Policy, Canada Research Chair in Law and Medicine,
McGill University

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DR. GUTMANN: Commission members, please be seated. Welcome back, everybody. We are about to welcome Dr. Bartha Knoppers. And Dr. Knoppers will speak with us about consent and return of research results.

Dr. Knoppers is the director of the Center of Genomics and Policy at McGill University in Canada. She has served as the chair of the International Ethics Committee of the Human Genome Organization and as a member of the UNESCO International Bioethics Committee which drafted the Universal Declaration on the Human Genome and Human Rights.

Dr. Knoppers co-founded the International Institute of Research in Ethics and Biomedicine, the Population Project in Genomics and CARTaGENE, a database of in-depth information on over 20,000 Quebecois. She has served on the board of Genome Canada and is a member of the scientific steering committee of the International Cancer Genome Consortium.

Welcome, Dr. Knoppers.

DR. KNOPPERS: Thank you. You'll note that consent is absent from my title but it is a leitmotif that you'll see in my sort of tour around the world. I was asked yesterday to put United States in my international perspective so my first three slides will be a brief resumé of what is happening with respect to consent and return of results and findings in the States.

Now, you've heard from Professor Wolf whose article on the consensus statement in a project specific to return of results came out this year. And the consensus statement of which I was a member was a rather -- it wasn't fractious, but let's say that we had spent a lot of time trying to reach consensus so it's not unanimous, but it did create three categories of should offer under certain conditions which I know she spoke to you about, may offer or not return.

And the conditions that led this group of researchers to come to those conclusions of three categories were also based not only on philosophical and legal considerations as well as clinical but on genetic epidemiology and the findings of certain scholars who in their research had attempted to at least by 'binning' findings provide some guidance to policy wonks such as myself as to how to actually make policy that could work and what kind of guidance could they provide. So again you see in these three bins pretty well a reflection of the three categories that that project came to.

Now, in addition even if you make it past the policy and you base it on scientific 'binning' as epidemiologically validated, you still need to have in most projects not an IRB but an informed consent -- this is just a name -- oversight board. And this is because most researchers or those in the research, even a multidisciplinary research team are researchers. They are not necessarily always clinicians.

And even if they are clinicians they may not all be cognizant of the particular condition. They will be in what they're looking for, breast cancer for instance, but they may not be on the clinically significant incidental findings that they see, that are staring them in the face when they do next generation sequencing, including both whole genome and whole exome. So this particular model of an informed consent oversight board then would serve to guide researchers and IRBs in their discussion on what to do with return of either individual research results or incidental findings.

And this comes from Kohane and other authors in Boston, and they've recently in an article that just came out also gone further in a 2012 article, but I've cited the 2010. They've actually incorporated in a dynamic way if you like participant preferences, attitudes and perspectives on return of results which can be culturally influenced by religion, by values, by age, by socioeconomic status, by having health insurance or not, et cetera, et cetera. So this is the three sort of sweeping changes that are occurring right now in parallel here in the United States.

I would however, like to take you back to a problem of a lexicon of definitions of terminology in return of results and incidental findings. So you see a lot of weeping and wailing in the Tower of Babel slide and this is because if you look at the literature you'll find that there is a conflation. People do word searches. You know, it's nice, great, computers exist. Put in results, put in return, put in findings and you'll say this country does that, so many biobanks do this, yes/no with little check marks and nice tables that fit well in scientific journals. But it's totally conflating different points of communication with different kinds of results at different moments and different kinds of research.

So you have your feedback for exclusion/inclusion criteria at assessment when you're a participant/patient involved in research. At a certain point in time your tissues, your samples, urine, blood, whatever, might go over the threshold, what's called -- or under -- a critical value when it goes to a lab. A critical value of such life-threatening significance that no matter what choices you made or what kind of research you're in you're most likely to be called back and be warned about your health status.

And then we have the general obligations that's existed since the Declaration of Helsinki, to return general research results. Usually this is done via publications that most patients and so on -- actually patients do, are probably pretty savvy, but let's say that most of the population would not be aware of.

Then you have the obligation of researchers in some studies who have access to biobanks for instance to return their enriched results. Biobanks simply being resources that are there collected for other researchers such as in the International Cancer Genome Consortium where we create data sets and so on. And you can use it if you return the data back so that the next user will not make the same mistakes or come to your erroneous or successful conclusions.

And finally the issue that I will address which is the individual return of research results, though this is a misnomer because research necessarily is the search for generalizable knowledge. It's not

about individuals, it's about groups, whether by disease status, by population, or subpopulations or whatever. But from time to time there are individual research results that do appear and what is the duty or not to return those results.

So I have five models. I'll start with the muddled model. This is Canada, okay? So the muddled model, this is very recent, December 2010, creates an extremely wide, completely uninterpretable obligation to return material incidental findings with significant welfare implications for the participant, health-related, psychological, sociological, and so on.

Unless you're in clinical research where the clinician is the researcher and may also perhaps be the physician, so you're in a patient setting, it's very rare that a researcher would know what the welfare -- broadly writ -- implications are for research participants. So this is a totally ambiguous, way too wide obligation, ethical obligation. And participants are supposed to be informed of a plan that will detail how that's supposed to be done. And I can tell you in Canada that we're still muddling in this model.

So let's look at Estonia then. Estonia is one of the countries in the world that actually has legislated for the creation of what's a national biobank. Now, national biobanks come in different forms. This one is where people go in to see their doctor. And in Japan, and I can go into other countries but I won't. So these are countries that have decided that as patients avail themselves of the healthcare system they can be asked to participate to contribute data and samples to a biobank.

But they are protected. In Estonia they have a law and there's different kinds of rights, there's different protection for data and access leaving the country and so on. And when they say genealogy, just in case there's a question, they mean paternity. It's just a very broad way of mentioning that. So that's what I call an integrated model. It is a model where citizens, whether patients or participants, actually go to a

physician and it would be part of their medical care. And so obviously results and the return thereof are personalized as they become available and meet all the three criteria that we saw in the first slide.

Then there's Sweden. And all these countries that I mentioned, Canada onward, have universal healthcare systems. So we're not in inequities in terms of what kind of healthcare may come from the return of results.

So Sweden then has a biobank 20,000 and they take -- it's a call to citizens to come forward. Asymptomatic, not yet ill citizens who simply contribute their data and their samples over time in a longitudinal study which then serves as a resource for other researchers to do clinical disease kind of research.

They do make what I call the exceptional model. They do say there may be cases where it's preventable, serious or life-threatening then they will go on a case-by-case basis and perhaps communicate results not to patients but to citizens participating in a biobank who then obviously become patients if all these conditions are met.

Now the Public Population Project in Genomics and Society which is a regrouping of 43 large biobanks around the world, most of them not disease-specific, but rather collections of material and data over time, longitudinally, in order to be available for focused disease-based research recently came up with a statement which is unreadable and deliberately so for you. It's that whereas most of the countries who use the generic consent model provided by P3G because it's longitudinal and it's a resource, it's a biobank, it's an infrastructure, it's not a disease or clinical study, agreed, consented to a broad consent. So not the open internet consent. And by the way, I've never seen a blanket consent, legal blanket consent since 1978.

A broad consent that is based on three pillars, and most of these national biobanks have three pillars. They have a heightened security, they have delimited the zone of the research to biomedical

research. So it's not to anything goes. And they have a heightened governance with ongoing review by REBs of who's been accessing them, what's been happening, and so on. So there's oversight governance, a heightened security and a biomedical range that is consented to. So this is the systemic model.

So P3G and this just came out 2 weeks ago, how do I put it, qualified its no return results just like I think the UK biobank will probably be doing, saying that there may be cases even in longitudinal studies where you do want to change your mind because the researchers using your resource are doing next generation sequencing and they're going to have interesting things. And you're doing a longitudinal. You can re-contact. Longitudinal means you have an automatic re-contact mechanism and there you may want to change your policy.

So my last model is one that's been severely neglected except in Europe and a little bit in Canada, and that is what happens for pediatrics. And this is what I call the dynamic model and it's my conclusion. The pediatric community as you know is a highly -- I must say relationships in pediatric research or pediatric clinics are usually very close. However, in this study that I did of 65 consent forms in Canada, pediatric consent forms, we found there was a whole range of promises what to return, not to return, and so on. All of these clauses came before the 2010 muddled statement that you saw earlier.

So in a consent that I did for a pediatric project on rare diseases we said obviously there has to be a plan, that's -- Canadians now have to have a plan for communication. But we made a specific exception for pediatrics. Contrary to literature emerging from here parents are not allowed to choose not to receive incidental findings of clinical significance if they are actionable, i.e., preventable or treatable, during childhood. Okay, so we're not talking late onset. In other words, the normal choices that parents have for their children cannot be exercised in the pediatric context when it comes to those kinds of findings. It would be considered neglect.

And this has just been taken up by the European Society of Human Genetics. They took the same position, that parents have a limited right not to receive this kind of information.

So in conclusion, as a law professor and a practicing lawyer I argue for guidance, not regulation, except I would agree with the earlier speaker for mandatory data security. Generally, however, in these fast-moving fields of genomics and emerging technologies, NGS today and something else tomorrow, guidance that can be updated and scientifically immediately valid and useful is the best way to frame a genomic research.

For return of results those same criteria remain, validity, utility and actionability. Keep it simple. Distinguish context. Distinguish population from patients from pediatrics, from incompetent adults and so on who are more vulnerable. And you don't need to elaborate. The principal level is the way to keep it so that responsible researchers and their IRBs and their institutions can actually exercise their professionalism.

And any narrow interpretation will do more harm to science than you can possibly imagine, particularly international collaboration and data-sharing which is extremely important considering the public investment in genomic research, that you be able to gain statistical significance by not putting barriers around the international sharing of data. And sorry about the PS. I can say it because I'm a lawyer.

(Laughter)

DR. GUTMANN: No apologies necessary. We're going to catch up and get back on schedule. So you're going to have a hard stop at 11:30. And I see Anita Allen's hand up so we'll begin with Anita.

DR. ALLEN: Okay, thank you. And I want to start sort of toward the end of your presentation. It was interesting what you said about the approach you took toward children where the parents

don't have a right not to receive the results of research where it could help the child during childhood. And I'm just sort of wondering about that line because I'm thinking about families that have children with disabilities where the children's relationship with the parents goes on far beyond childhood.

And even just thinking about the fact that there's so much family interdependency, that if you have a health issue in a family just because you might be 27 when it first arises doesn't mean that mom and dad aren't going to be there for you and be involved in your care.

So I'm just wondering why would you draw that line at, you know, conditions that would develop during childhood, knowing the reality of interfamily dynamics and connections, especially in the context of disability or even just simply in the context of ordinary family life.

DR. KNOPPERS: I think there's no doubt where there's other -- and I put quid at the bottom of one of my slides. When you're dealing with -- I put quid, incompetent adults, shouldn't the same hold true. I could have put quid, dependent disabled persons, shouldn't the same hold true. So when we're dealing with vulnerable -- I could probably say yes to what you're saying.

However, for children and I'm only limiting myself to that category, as legally defined parents have authority till legal majority which they are bound to exercise. And for that reason when you create a professional norm which then becomes the standard of care you have to be very careful that if you're going to create other norms, and I agree with the areas that you would like to extend this particular norm to, that you don't create legal obligations because professional standard of care becomes a legal obligation that you cannot meet. So, I do agree that it could and should be extended. In this particular project we were only dealing with minors.

DR. GUTMANN: Jim?

DR. WAGNER: Actually I was going to -- already in transition because it's not necessarily hard stop we get to keep her here.

DR. GUTMANN: Right. We have 5 more minutes.

DR. WAGNER: Then let's get other questions. I'm sorry.

DR. GUTMANN: Other questions. Any questions from our audience?

DR. KNOPPERS: Could I make a comment then? I have 3 minutes.

DR. GUTMANN: You may.

DR. KNOPPERS: Yes. I'm really concerned about the language around informed consent. I mean, my lexicon was on the return of results. A blanket consent is language that should be barred from any considered document because I've yet, as I said, I have consents going way back, "I give my DNA to science." That's a blanket consent. I haven't seen one of those for the last 15 years.

I have seen broad consents. "I agree to give my data and samples for future unspecified research," that's usually the language, "provided the following conditions are met." And then you get annual IRB review, heightened security measures as described in the consent. And the other one is the -- for biomedical research.

The open consent which was mentioned earlier which has to do more with the kind of virtual environment is different. And so -- and specific consent is usually disease-specific. I have seen consents that say cancer and related conditions, and that's good too because we don't know whether hypertension, you know, or what kind of cancer, you think it's breast but it's ovarian. You think it's cancer but it's diabetes and cancer together. So we have to be very careful not to make lists with options. One, it's unworkable and two, the kinds of options that people usually want create difficulties for data-sharing and for scientific research. They usually check them.

DR. GUTMANN: Could I follow up on that? Yes, I see, and Christine may want to as well. So, if you take the view which Christine has articulated and I think we can agree to that consent doesn't carry all the moral weight. So let's just say consent is a necessary but not a sufficient condition. Then I wonder why let's not call it blanket, but a broad or open consent, what would be objectionable about that if somebody herself feels that it's fine to use my information however you would use it provided there are other conditions placed on the ethical use of it. In other words, within the other parameters that are established I myself do not want to add any. Is there --

DR. KNOPPERS: Perfectly valid. And if you look at the Personal Genome Project, I mean they actually give an exam before you're allowed to consent. If you look at the consents, the portable legal consent from Sage Bionetworks it's extremely detailed. So even these so-called open because they're on the open net and once you say yes you're out there, that's what's -- you're opening your broad consent and everything that comes from it to the public domain. That's the open part.

DR. GUTMANN: The converse I would say is also true, that even with the other strictures you still want to get people's consent. I mean, you don't want to do this without consent.

DR. KNOPPERS: Absolutely.

DR. GUTMANN: Christine. And then we're going to stop.

DR. GRADY: Thank you and some of what I wanted to ask was what Amy just asked. But I have a question, almost the question that you asked earlier. Do you think that there's a role for any opt-outs?

DR. KNOPPERS: I've seen -- two answers. I've seen opt-outs because I used to offer them and I had to re-consent 10,000 people because they couldn't remember what they'd opted out of or opted

in for, or they cross-opted. Like they did contradictory choices. So from a practical point of view it ended up being a real --

DR. GUTMANN: Just give an example of that.

DR. KNOPPERS: Okay, breast cancer. I was in a big breast cancer project and the choices were do you want to receive results. No. Do you want to receive results - yes, then the choice was you, yourself, or your physician. And then there was another box. And some crossed all of them, the no, the yes to me, the yes to my physician. And so it was -- the ethics committee loved it but it was totally unworkable.

DR. GUTMANN: Surely computers should be able to prevent, lock out -- so it might be -- I understand. I'm just adding.

DR. KNOPPERS: You have to remember not the whole -- there's half of our population anywhere is not computer-savvy around computers.

The other opt thing that is really bad is when you give people choices about what kind of research because they -- you either do it in a -- there will be no biowarfare. There will be no cloning. So, in other words that's -- then people come up and they say to you oh, you mean cloning is really going on? Is it possible to do biowarfare with my genetic material? So, either from a practical point of view or from what you create as an image of research by saying we will not do this and we will not do that, we will not do that, therefore your broad consent is valid because you know exactly how narrow we're going. You create a perception of all the wrongs as opposed to the -- presumed or hypothetical wrongs as opposed to the benefits.

DR. GUTMANN: Thank you. Thank you very much, this is extremely helpful and we thank you all -- all of us thank you. Thank you.

(Applause)