Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I am Bob Barrett. In the past ten years there have been a number of high profile legal cases that have involved the use of human specimens with each case containing an argument over whether the research subject had been properly informed and how their specimens were going to be used in research.

With the publication of Rebecca Skloot's book, *'The Immortal Life of Henrietta Lacks'* about a woman who unknowingly provided the first immortal human cells grown in culture, the topic where informed consent is now being discussed by book clubs in living rooms and coffee shops across the country.

In the April issue of *'Clinical Chemistry'*, a question and answer article titled 'The Use of Human Tissues in Research: What Do We Owe the Research Subjects?' summarize the opinions of four experts representing different views of the subject of informed patient consent.

Joining us is the lead author Dr. Ann Gronowski, an Associate Professor in the Department of Pathology & Immunology at Washington University School of Medicine in St. Louis, and Bioethicist Dr. Arthur Caplan, the Emmanuel and Robert Hart Professor of Bioethics at the Department of Medical Ethics at the University of Pennsylvania.

Dr. Gronowski, why do you think that this topic has gained such interest recently?

Dr. Ann Gronowski: Well, the book that you mentioned *'The Immortal Life of Henrietta Lacks'* has played a big role in generating discussion about the use of human tissues in research. In addition to detailing the story of Henrietta Lack the book also describes some of the early history that has shaped the consent process that we have in place today, in, I think, easy to understand layperson language.

The other thing that led to discussion is publicity over several high profile legal cases that have led to the destruction of patient specimens. The first case involved over five million leftover dried blood spot samples that were collected for newborn screening by the Texas Department of State Health Services.

According to a lawsuit, it was filed by five plaintiffs; the State of Texas had been retaining the blood samples from newborns since 2002 for use and research. Well the plaintiff claimed that the Texas Department of Health Services violated their rights under the Fourth Amendment to the constitution to be free of unreasonable searches and seizures because specific consent was not obtained for the indefinite storage and undisclosed research.

The plaintiffs also claimed that the blood spots contain deeply private, medical and genetic information and that the defendant's retention and use of those samples violated their right to privacy and liberty under the Fourteenth Amendment.

In response to the lawsuit, the Texas Legislature enacted a law governing the collection of newborn blood samples. Now the law states that the Department of State Health Services can retain a leftover material for research as long as parents are given an opportunity to opt out by filling out a destruction directive.

Shortly thereafter, the lawsuit was settled and the Department of State Health Services agreed, in my view tragically, to destroy all the remaining specimens in their bank. In the second recent case, members of the Havasupai Tribe in Arizona sued Arizona State University. The tribe alleged that in 1990 they had consented to the use of their blood samples for diabetes research. But instead their DNA was utilized for studies on schizophrenia, metabolic disorders, alcoholism, inbreeding, and population migration.

The tribe's main complaint was that the researchers failed to get informed consent for these other studies. Recently, the university's Board of Regents agreed to pay $700,000 to 41 tribe members and provide other forms of assistance to the impoverished Havasupai tribe and to return their blood samples. So both of these cases were very high profile and received a lot of popular press.

Bob Barrett: What went wrong with the consent process in these cases and how can things like this be prevented in the future?

Dr. Ann Gronowski: In both of these cases, the plaintiff's chief complaints were that the researchers were not transparent about what they intended to do with biological specimens and did not obtain the proper consent. Because they were settled privately before court rulings, we don't know how a court would have ruled on the plaintiff's allegations. It is very likely, however, there was greater transparency about what the researchers intended to do with these specimens these lawsuits could have been avoided.

Bob Barrett: Currently are all researchers required to get consent for all human specimens?

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Dr. Ann Gronowski: No, actually they do not. In the United States the regulations that pertain to human subject protection and research are contained in what's referred to as the common

rule which is the section within the law governing all federally funded research. The common rule does permit research without the subject's consent in certain circumstances. For instance, if research is conducted using unidentified or de-identified samples and the researchers do not have access to patient's private information, then this research does not require informed consent.

Furthermore, individual Institutional Review Boards or IRBs have this question to wave or alter the informed consent requirements if the IRB finds and documents that, one, the research involves no more than minimal risk to the subjects.

Two, the lack of consent will not adversely affect the rights and welfare of the subjects.

Three, the research could not practicably be carried out with specific consent.

And four, subjects will be provided with additional pertinent information after participation.

In the Havasupai tribe case, this subject had given consent for the use of their specimens but their lawsuit was based on the fact that their samples were used for other types of research that they did not consent to.

Researchers must provide subjects with an explanation of the purposes of the research in the expected duration of this subject's participation. General descriptions are not sufficient and descriptions should be studied specific. This is because research participants can't give "informed consent" if they are not adequately informed about the intended purposes and scope of the research.

In the Texas case of the newborn dried blood specimens, these were leftover specimens. The law would permit them to be used by researches if they were de-identified. But because genetic testing was being performed and the names retained they were not de-identified. In my opinion the solution should have been to permit research using coded non-identified samples rather than to destroy such a valuable biological resource.

Bob Barrett: Do you think that the patient should retain the right's disbursements or sharing the financial gain of the research?

Dr. Ann Gronowski: This is a popular question, Bob. I believe that patients should be informed if they will or will not share in any financial gains resulting from their tissue donation at the time they give consent. It's then their choice, if they want to give consent for the use of their tissues or not, it's all about

being informed and having choices. But researches cannot use blanket weavers to get that consent.

Bob Barrett: We now turn to Bioethicist Dr. Arthur Caplan. From an ethical standpoint doctor, it seems that we've become more stringent about how researches can obtain specimens from human subject. What has changed?

Dr. Arthur Caplan: Well I think over the years really, over the decades, we have seen increase in emphasis on informed consent from the subject that you have to get informed consent in order to get access to bio-specimens, and then informed consent has to be very specific, meaning, it has to describe exactly what you're going to use it for. So a very strong tightening up of informed consent requirements, if you will what used to be treated as biological waste and just available to anybody who wanted it is now seen as something of value and you need permission to use it.

And I think many researchers and many institutions are seeking consent also to follow up with subjects over time so if they want to correlate information from medical records over time with biological specimens and genetic information, they are asking specifically for permission for that, and most places ask subjects now to announce any claims on inventions or discoveries that might came on to their work with these biological materials or genetic information that might turn out to be profitable.

So consent has really picked up tremendous amount of force and emphasis moving to very specific areas like what do you propose to do, who long you are going to keep my specimen and how long you're going to follow me, and am I going to get anything if something of value is made?

Bob Barrett: Well that goes into the next question which is, how do you feel, should researchers be required to get consent for biological specimens, or do you believe in the concept that human tissue is a common heritage of humanity be used for the collective good?

Dr. Arthur Caplan: I think it's nice to get consent certainly you needed when you are trying to obtain materials. But the idea that you are going to get people to wave off any claim on property or any claim to take a share of something valuable that's made a genetic test or some type of treatment that might eventuate, I don't think that's going to hold up in the long run.

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I know a lot of programs are using these open-ended consent forms to say whatever happens down the road, you

won't make any financial claims against us, but I think that's too vague and too incomplete to really hold up, I think bluntly courts will laugh at that if those kind of consents get challenged.

So if you don't know the details of what is going to happen down the road asking somebody to wave off their rights, asking them to consent to something that needed a research or they really understands in terms of what might be found, what profit might be made. I don't think it's going to hold up, it's binding or legally stand up to court challenges. So even though informed consent has grown a great deal in importance, so I think it's weak in some areas like control over biological material.

I would actually prefer to see us move more toward a framework of gifting. We use gifts as a framework when people donate their organs and tissues for transplant. We don't actually say to them, we will give your liver to person X, and is that alright with you? We ask them to altruistically make their tissues and organs available for transplant, and then since it's a gift they renounce any control over what is done with those gifts or what happens to those gifts. The gift framework in other words makes it clear that commercial interest is going to be forgone. You're just not going to be able to do it because you're giving the thing away.

It also means that future use and what happens to the organs and tissues is open-ended and that you've transferred as the donor possession of the organ or tissue to the third party that's asking for them and you're giving up all control.

So I actually think, even though we started off down the informed consent path because people were looking at bio-banking and genetics as research topics, I think we got off on the wrong foot. I think a gift approach makes better sense as long as it allows the opportunity to someone to say, well, I don't want to make a gift, I don't want you to have my tissue. But once you get to that framework, I think it's important to understand that you have pointless trouble facing you in terms of commercial claims and anything of value or have any role and re-consent the person again-and-again if you see new studies that you might want to do with biological specimens.

I think a gift framework unfortunately is the one we should be using but it's not the one we are using.

Bob Barrett: Well do you see more changes coming in bioethics in regards to patients giving consent for use of their specimens?

Dr. Arthur Caplan: Well, I'd like to see a shift into that gift framework but we are so far down the road or relying on inform consent to specific research use that that just may not prove possible. But I do think one other path may open down the road, and that is using more anonymization, by that I mean coding and disguising the identity of the people from which bio-specimens are taken.

If you then retain links to identifying information but only make those available to third-parties, then you may have a dataset that researchers can't figure out, the identity of anybody. But if they need to go through a third-party to link it to health information or personal or private information as part of the research they want to do that may make sense.

So I am looking toward may be not the optimal solution which might be changing over to a gift framework but the next best solution and what I think is going to come is a greater reliance on anonymizing bio-tissue samples as we collect them.

Coding linked information, putting that in the hands of third-parties whom researchers would then approach to get links back to the anonymized bio-specimens. But researchers would never have the identifying information of cells and then wouldn't be in a position to be able to harm or violate the rights of anybody who had donated tissues.

So it's a long windy road, anonymization. If you are going to retain links it has to go into the hands of third-party people not the researchers themselves, but I do think that probably would permit most of the research to get done without trying to go back and consent somebody every time you want to do a new study.

Bob Barrett: Well now we get to the concept of de-identified specimens, meaning the specimen comes to the researcher stripped of things like the patient's name and address and hospital number. Do you think that making specimens de-identified really alleviates the risk and ethical obligations to the subject?

Dr. Arthur Caplan: I think de-identification or anonymization really does help a lot. Even though it's possible to track back and decode the identity of sources that's called Linked Anonymization or Linked De-identification. The very process makes it clear that the privacy and confidentiality of those who make bio-samples available, genetic information available or data available is expected and you are going to do what you can to protect their anonymity.

So if you have the information linked by some type of coded algorithm then I think you are going to need to make sure that people trust whoever it is that holds those codes.

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If you are going to break them you probably going to have to have some third-party board may be made up of researchers and patient advocates to establish when re-linking could occur to de-identified or anonymized information.

If you are going to have to be trusted third-parties in other words, who could may be break a link if you thought, hey, there is something that might benefit people that you find ten years later and you want to go back and tell them, you are at risk of a disease but we now have a medicine that might help, or if you want to open up an entirely new study, you don't want to go back and find everybody from the original set of people who gave you materials but you are going to protect them because only the trusted third-party will have the actual identifying information.

So I think de-identification and anonymization, if they are also linked up to creating trusted third-party data holders really would work to solve a lot of the ethical problems that now confirm bio-banking research.

Bob Barrett: Well finally Dr. Gronowski, based on your interviews with experts in the field what have you learned about the patient consent process, in other words what do we owe the research subjects?

Dr. Ann Gronowski: Interestingly despite the very background of the four experts interviewed in my article their opinion had much in common. They all felt that protection of subject privacy and confidentiality is of the utmost importance. In cases where subject specimen data can be linked back to the patient then subject should be asked to give consent, and genetic information should be viewed as linkable.

The four experts would also agree that more guidance is needed for researchers on how to properly consent and protect subjects as we move into the future.

Bob Barrett: Dr. Ann Gronowski is an Associate Professor in the Department of Pathology and Immunology at Washington University School of Medicine in Saint Louis.

Dr. Arthur Caplan is the Emmanuel and Robert Hart Professor of Bioethics at the Department of Medical Ethics at the University of Pennsylvania.

They've been our guests in this podcast from Clinical Chemistry. I am Bob Barrett, thanks for listening!

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