



**Presidential Commission**  
*for the Study of Bioethical Issues*

TRANSCRIPT

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DR. WAGNER: Greg Biggers and Leonard D'Avolio, if you would join us up here?

DR. GUTMANN: Thank you all. I think members of the Commission will be soon seated. So I'll start with my introduction.

Continuing on genomic privacy and data access, Greg Biggers, welcome, serves on the Council for Genetic Alliance, which is a leading non-profit health advocacy organization committed to transforming health through genetics. And Mr. Biggers is representing Council for Genetic Alliance here today.

He is also the CEO of Genomera?

MR. BIGGERS: Genomera, that's right.

DR. GUTMANN: Genomera. Serves on the boards of an elementary school and a community development organization and advises technology start-ups. Welcome.

MR. BIGGERS: Thank you.

It's a privilege to be here today among such esteemed hearts and minds. Thank you for inviting me.

There is a new tide coming into the harbor of health research. A tide of empowerment for the people that doctors call patients. At Genetic Alliance and at Genomera we tend to just call them people.

(Laughter.)

MR. BIGGERS: And this tide provokes some new ways to think about control, power, trust and engagement. And I'd like to tell you some stories that relate to those themes. As some of you probably know, Genetic Alliance is more than just an advocacy group. Genetic Alliance is a network of networks. It is an advocate for advocacy groups and individuals with broad reach through over 1,200

condition-specific organizations. So we feel the burden and the power of these people, many of whom live in the community of the diagnosed every day.

And this is one of those groups, PXE International, it serves a group of people affected with a rare condition, pseudoxanthoma elasticum. PXE International was one of the pioneers of patient-driven advocacy, control, and research. And it's really a remarkable family that begins -- excuse me, a remarkable story that begins with a family with two affected children. Disappointed and shocked that there wasn't more known about this disease, the family began to get involved. And ultimately created this non-profit organization, a patient-run advocacy and support group with pretty remarkable accomplishments.

PXE International found the gene responsible for the disease. They created the first patient-run bio-bank and they are driving research on new treatments. All of this with the affected people, the patients, the people, at the center wielding their power for research, and fueled by the trust of the community of the diagnosed.

PXE International and groups like it are part of this new tide of empowerment. These groups demonstrate practically, operationally, not only philosophically and academically, what we can accomplish with the trust and cooperation of a community. And Chris Saha picks up that theme in this piece in *Nature* where he and his colleagues argue that "the path to impact, while respecting research subjects, lies not just in changes to the Common Rule, but in forming new kinds of relationships with research participants by inviting them to be participants and not just subjects, and by treating them as partners in research."

And growing communities of trust like that is what the Genetic Alliance Biobank Initiative is doing. It's replicating much of the model that was proven by PXE

international and helping people create participant-run, by a bank's registries and research consortia, where the locus of control is with the participants, the patients, the community of the diagnosed. Where decisions are made and control is exercised by principles of community governance rather than a single or serial consent event.

And it's those kinds of models that the authors endorse in the piece, in this recent piece from *Nature Reviews Genetics*. They call them "participant-centric initiatives." Initiatives where people are experiencing a transformation in how they think about themselves in relation to the health research enterprise. Going from N is someone else, I have a question about my health, I have a disease problem I'm looking to solve, and I hope that someone out there who I will probably never meet is a subject in a study, the results from that study will be published and I or my doctor will read about that and will know what to do. And they move from there to N equals me, as more and more health becomes digital, people have access to data about themselves, and they're exercising curiosity and looking for discoveries as they interrogate that data about themselves.

In fact, there's a whole movement that is growing like fire around the world right now called the "Quantified Self". It's people -- some of them are diagnosed, some of them are just wellness enthusiasts, who are getting all this data about themselves and they're swapping stories about the discoveries that they're finding.

But the transformation doesn't stop there. Because people realize that, in order to handle anomaly and to achieve statistical significance on a population basis and to practice good scientific rigor, we have to work together. And so they come around to this notion that N equals we. That together, by participating together, we can advance research and discovery much more quickly than we've seen in the past.

When you combine this N equals we world with the connective power of the internet, some interesting things are possible. And at Genomera, we are helping people break open the bottleneck constricting the flow of research, do science together, and find new discoveries. Genomera has created a place where anyone can come with a question that health science could answer. And the company and the product helps people turn that question into a scientific health study and seek participants who follow the protocol on themselves and share their data for joint analysis.

In this case, it is really intensely participant-driven health research where people are self-forming now their own communities of trust and doing health science together. It's a place where the subjects have become the collaborators.

Another N equals we meets the internet project is "That's My Data." This is an initiative of people who are taking control of their breast cancer related genomic variation data from clinical trials and diagnostic tests, putting that collectively, deciding to put that data in multiple common style data repositories for use in additional research.

And the thing of note here is not the fact that this data can travel around and that it's going to have some use somewhere else, although that's all good. I think the item of note, the part that we can bring to a conversation here is that the locus of control in these actions. These are people saying, this is my data and I'm going to band together with some other people and collectively we can do something with that, exercising our own power over our data for further impact.

So we see across these examples that research roles are expanding and they're blurring. People are moving from subjects to participants to collaborators. And ultimately, as is the case with PXE International, patients, people are becoming shareholders in the benefits of research with a real operationalized stake. Not just in the

tissue and the data and the funding, but in the scientific outcomes and even the economic benefits of future therapies and intellectual property. Roles are expanding really rapidly.

So bringing the voice of patients and the community of the diagnosed, and people as we like to call them to the conversation, I thought it would be useful just to have a brief conversation about what do we want? You know, it's a bit different than the philosophizing that we've heard some of the day today, but I hope this can be useful.

So what do patients want? What do people in the community of the diagnosed want? We want control, we want influence over tissue and data and intent and outcomes. And yes, of course you have to ask us if you want to use our tissue or data for something other than the original purpose.

But we want trust. We don't want to do this in an environment of conflict and tension. We want trust that requires engagement and a conversation and requires bi-directional communication. And when desired, we must return results to participants. And of course, we want impact, that probably goes without saying. In our communities, we are constantly asking ourselves, as we think about how to govern the activities we're trying to influence, what is at stake here?

We want research to flourish and we join in common cause so that we can make a difference. And we will be shareholders in the benefits, including the future economic benefits because we are already shareholders in the stakes and the risks, aren't we?

And so -- and I think this last point actually is the summary of everything that's on this list, and everything I've said so far this afternoon. Which is this, that we want to express our rights and our desires in addition to having them protected. And it's

exciting that there are now the tools and policies that enabled this to happen.

So we're speaking this afternoon about the future of genomic data and participation in research and things like that. And a few famous people have said some kind of witty things about the future. Buckminster Fuller, his opinion was that you can't change anything by fighting current reality, you have to do something new. And so we are building new models for research collaboration.

Alan Kay, a famous futurist and confidante of Steve Jobs, among many other things, said the best way to predict the future is to invent it. And we are inventing the future right now.

And then finally, William Gibson, you know, the kind of popular cyberpunk novelist said, the future is already here. It's just not evenly distributed yet. And so there is this new tide of patient empowerment provoking questions about equity and equitable behavior in health research. And we believe that answering those questions in a participant-centric manner is the key to accelerating both individual and public benefit.

But I would go further than Gibson's quote, actually. I think that there are multiple futures already here. And we, we in this room, we citizens of this nation, we citizens of the world, have the responsibility to choose which future do we desire? As this new tide fills the harbor, increasingly it is the participants, patients, who are piloting the ships of research, crewed of course by a diverse group of stakeholders. But the participants increasingly are at the helm, expressing our rights and our desires. That is the future that we would like to distribute.

DR. GUTMANN: Thank you.

Our next presenter is Dr. Leonard D'Avolio -- pronounce your last name

for me so I get it right?

DR. D'AVOLIO: It's D'Avolio (pronouncing).

DR. GUTMANN: D'Avolio. Right. And Leonard is the Associate Center Director for Biomedical Informatics for the Department of Veteran Affairs, Massachusetts Veteran Epidemiology Research and Information Center, MAVERIC for short, and also on the faculty at Harvard Medical School. He is responsible for several VA initiatives including the development of the infrastructure for the Million Veteran Program and the Department's Genomic Scientific Infrastructure to Enable Personalized Medicine. He is also the Informatics lead on the point of care research initiative, which is developing new models for the conduct of science, including the incorporation of clinical trials into electronic medical records systems.

He's also an investigator on several projects focused on finding patterns in clinical data, the future of the electronic medical record and the upcoming challenges of personalized medicine. Thank you very much for being here.

DR. D'AVOLIO: Thank you. And thank you for having me. It's quite an honor to be able to represent the work of so many within the Department of Veterans Affairs on behalf of the United States Veterans. So thank you.

So in an effort to simplify in the most extreme manner possible, the next two slides are the United States health care crisis. Number one, we're not doing great, and number two, we're not getting what we pay for. And so a bit of context helps in lining up why new models of learning are required. And it's a great privilege to be able to get this panel thinking about some of the new bioethical challenges that these new models present, some of which you're already more than familiar with. I hope that I introduce some new challenges to add to your already full plates.

So very quickly, MAVERIC is 130-person multi-disciplinary research and development center within the Department of Veterans Affairs. We're located in Boston. Our goal is to create a learning healthcare system within the VA for the application of research resources and methodologies to important clinical problems.

So I'll talk a bit about some of the larger projects that are novel in nature, and also presenting some significant bioethical challenges worth consideration.

First is the Million Veteran Program. Within the VA, I think that there is a unique opportunity here. Of course, the opportunity of genomics and personalized medicine is one that's available to all of society. But the VA is uniquely positioned to capitalize on personalized medicine. Number one, the VA is a payer system. We pay for the care we provide. So we invest in understanding how to provide that care more effectively.

Number two, the VA is the second largest national funder of biomedical science. And so to capitalize on our existing investments in science, there is an opportunity here to create an infrastructure that is re-useable. We are an intramural research program, which means that if we create this infrastructure, we can make sure that it's used by all investigators that are taking funding from the VA.

And a really nice benefit of doing a research within such a large healthcare system is that there is potential to advance medical knowledge for all of society. We have six million, quote, unquote, active users of the VA healthcare system, those are folks that have used it in the last two years, and twenty-plus years of longitudinal electronic medical record data.

We also study whether or not the veterans agreed that this was a good idea, and 83 percent of veterans support the idea of a genomic database, 71 percent said

they would definitely or probably participate in such a database.

So the Million Veteran Program was created. The goal, one million veteran volunteers in five to seven years. It's not really a study, per se, it's a cohort gathering effort so that other studies can capitalize on that investment. So it's a survey, a five-page baseline and then a follow-up fifteen page comprehensive questionnaire. There is a blood sample, it's open consent, so informed open consent which means we can reuse that information for multiple studies. And then HIPAA authorization, full access to the electronic medical record and the ability to recontact veterans in the case that we need more information than we currently have.

Some logistics, 40 facilities enrolling, scaling to 55, mail to every veteran. Surveys and scheduling happens by mail, but the consent and blood draw is in person. There's a call center to answer questions.

Heavily automated by necessity, there are just some of the numbers. Right now we're doing about 2,000 samples a week. Yesterday we processed 600.

Here's sort of a cartoony representation of the information system that makes it all possible. We call it GenISIS because we are in healthcare and part of the government, so we use long and snappy acronyms whenever possible.

(Laughter.)

DR. D'AVOLIO: There is a secure scientific environment from which researchers can remotely access and do analysis on that data. The governance and access policies are right now actively a work in process, but I would like to make note that this is -- the DNA biobanking is not new to the VA, and there's a wonderful paper that outlines what we're doing. This is back in 1999 we first started gathering DNA for reuse as part of the VA's cooperative studies program, DNA biobank. We're over -- we

might not have 55,000 yet. We're close to 55,000 samples in.

These should be familiar bioethical challenges to the folks on this panel. I think rather than go into them because they're more than familiar, I will say that we dealt with them in a slightly different scope. So many are working on what our responsibilities are related to emergent findings. But what our -- how do we handle those responsibilities in the case that we have a million veterans becoming part of this program? And I think the country has about 3,000 geneticists at this time. So there are some real problems of scale when it comes to addressing our bioethical challenges.

I'd like to hop from discovery of genomic data to clinical effectiveness, not just of genomic data but in general, we have a real information dearth. We have a data overload but an information dearth in healthcare. And that's why I talk about new models of science.

Clinical effectiveness is not covered. Our two methods of evidence gathering right now, we have randomized controlled trials, which if you have years and millions of dollars can answer a few hypotheses with highly controlled data and the power of randomization. And we have observational studies which can do larger Ns at smaller cost, but obviously suffer from bias.

So what is actively -- what is actually in place right now in Boston, Providence and soon to be Baltimore is a new program that's intended to be national in scope. It's the point of care clinical trial program or point of care research program. The idea is a clinical trial with the substantial portion of its operations conducted by clinical staff in the course of providing care.

So this is the current model of conducting clinical science. Cohort identification, enrollment, consent, randomization, intervention, data capture, analysis,

and then by some studies, 17 years later, an actual translation of that finding.

What I'd like to draw attention to as being novel here is everything in the gray -- I'm colorblind, so I'm not sure how exactly that's appearing to you. It was gray on my computer. But everything in the gray are the activities that are now conducted as part of the point of care clinical trials program in the electronic medical record automatically. And the only caveat to that is enroll and consent, which in our very first study involves a study nurse and an in-person informed consent. The two boxes in yellow are the only two that a study team is involved in under this point of care model.

To put this in lay terms, we have jammed a clinical trial into the electronic medical record. Our very first clinical trial right now is an insulin protocol. There is not compelling evidence -- there really isn't much evidence at all to suggest that weight base versus sliding scale insulin regimens are more effective than one another. Classic comparative effectiveness. These are two widely accepted treatments that are in the clinic right now. We don't know which one works better, and we're not going to do a very extensive clinical trial to figure it out.

So there is in all its splendor. This graphic is maybe not the prettiest electronic medical record out there, but I would argue one of the most functional. Because we were able to design this entire study within the 20-year-old VISTA System, which is the VA's electronic medical record, using existing functionality. And as a result, what we're doing at three sites can scale nationally.

The first option -- I understand that you can't read it -- the first option in the order menu under insulin options is, number one, no preference, randomize the patient. So these are some of the early numbers. I think the one worth drawing attention to in the short amount of time we have is that patients in general, only four

have declined participation out of 129 opportunities.

Doctors have been less enthusiastic. When interviewed, doctors are in support of the idea; I think a mistake we made in our first pilot is that our house staff rotates every three weeks. We're currently conducting focus groups and interviews of both doctors and patients to better understand the issues here and what they think of this.

And I think that this raises some very interesting bioethical considerations. What level of consent is appropriate? How best to obtain it? You want a program with minimal perturbation, but you want an informed patient. But there are some real questions here as to whether or not -- and this is for you to debate -- is this quality improvement? Because the system certainly will be engaged in continual improvement. Or is it research? And I think we're blurring the line and I like that. I think there's great potential in blurring that line and I hope you'll give us some guidance in how to do it most responsibly.

And I'd like you to consider when thinking through these issues, when we do quality improvement, consent is waived. There is no conversation with the patient. When we do research onto the model of cluster randomization, again consent is waived. So is the fact that we're learning from a quality improvement effort mean that we have to add engaged in research obligations to clinicians and informed consent to patients and at what level across the spectrum of confirmed -- informed consent and patient engagement?

My last couple slides are crediting all the people who have worked very hard to make this possible within the Department of Veterans Affairs on the MVP team, the point of care team, and to acknowledge the vision and support of the Office of

Research and Development for allowing this to happen.

DR. GUTMANN: Thank you, Leonard; thank you, Greg. And we're open to questions from Commission members. Who'd like to begin? Jim?

DR. WAGNER: Greg, I'm curious. Actually it's a question to both of you, but I think I saw the path more in yours Leonard.

How is it as researcher I could have the prospect of getting access to -- and under what conditions, to some of these participant run databanks?

MR. BIGGERS: Yeah, so the conditions vary depending on the people governing in the case of, you know, patient-run biobanks, in what they're interested in having done. And I think we have very early evidence that there are probably some market-like functions occurring. But because it's not widespread, I don't think we can say that it's necessary normative.

But I think you have some groups where they are in a position of such power because they have very well consented tissue and data and have an ability to have conversation with the people they represent for additional use. And they bring an agenda to the table, and so there's a conversation between them and a researcher about, okay well, how much are you willing to abide by our agenda? What are you willing to return? How long will your research be proprietary if it is proprietary? All these kinds of things. How much money would you like us to give you to help you do your research? There's a number of variables that affect a decision outcome in each one of those cases.

DR. GUTMANN: Do you want to follow up?

DR. WAGNER: Yeah, could I just -- a quick follow-up on that. So the assumption is in these participant-run databases, they are data assembled for at least a

general or communal purpose, not -- that goes beyond just protecting those data or controlling how those data are made available, but that there is -- in general everyone agrees that we are going to pursue something around -- broadly around diabetes or we're going to -- or broadly around movement disorders or something like this.

MR. BIGGERS: Right. So good -- yeah, good question. There and again, you know, I think the future is slightly here but it's not evenly distributed. And so I feel a little cautious about making generalizations, but I do see two categories. One category is condition or disease group run biobanks and data repositories. And in those cases, I can't think of one that doesn't have research as one of their explicit aims.

On kind of the more consumer-driven kinds of things like Genomera and other people are doing, it's much more varied.

DR. WAGNER: Okay. And Leonard, I'm just curious, are your data, because they're government collected data, are they publicly available?

DR. D'AVOLIO: That's a great question. In one of my bullets, and we went past it pretty fast, is what is our responsibility to contribute that data back to the public?

Right now the VA's current position on this, and actually we have a policy representative here who can answer any very specific questions, but the policy is that the data is not going to be shared back to a dbGaP because our responsibility to the veteran is to maintain their privacy first and foremost.

Who knows how policy will evolve over time as we learn more about it, but I think leadership has made the decision that, this time, because of the ability to reidentify from some of the slides and great talks we saw earlier, the Department of Veterans Affairs has decided that this data will remain in the VA.

Now I should make clear that researchers with valid scientific questions that are willing to go through the VA consent process will have the mechanism to come in and ask questions of this data, that's the governance as to how exactly that works, that's still being worked out.

DR. GUTMANN: So the consent, the open consent is consent to research through the VA?

DR. D'AVOLIO: Yes.

DR. GUTMANN: Christine?

DR. GRADY: So one of my questions was just answered. But I was going to ask Mr. Biggers, you didn't mention the word "privacy," and we talked about privacy the whole last hour and you didn't mention it once in your presentation.

MR. BIGGERS: Right.

DR. GRADY: I was wondering if that was because you mentioned control. Or can you say anything about the views of privacy on the part of the people that you were representing in your talk?

MR. BIGGERS: Yes. So and we often think in our communities as privacy -- about privacy and control being joined. That especially -- well, control can mean many things, but it's difficult for -- in our communities to have a conversation about privacy that doesn't usually involve a heavy amount of discussion about control. So that's probably one of the reasons I didn't mention it explicitly.

But I think another reason it didn't come out explicitly in the ten minutes -- and you know, of course you have to exercise some editorial control --

DR. GRADY: Sure.

MR. BIGGERS: -- but is that again, you know, generalizations versus

specificity generally speaking, and this is not always the case, generally speaking, the communities with whom we work prioritize progress in their conditions and in their diseases and in therapies generally above privacy.

Now privacy does become more important among a few stratifications -- stratified lines, and again this is coarsely speaking. It stratifies often by age of the participant and by stigma of the condition. But we see a general trend of let's figure out how we make progress and let's get the right privacy controls that allow progress to continue.

DR. GRADY: Can I ask another?

DR. GUTMANN: Sure.

DR. GRADY: I wanted to ask Dr. D'Avolio, what does the open consent allow the VA to do? And was that used based on any sort of way of evaluating whether the veterans were open to that kind of consent, or was it just used -- I mean, in other words, how did you decide to use it, I guess?

DR. D'AVOLIO: The reason we went with an open consent is because this resource is intended to be able to answer questions related to genomics and other types of -omics over time, across disease domains. And in order to make the most of this taxpayer investment in this cohort, we didn't want to limit it by disease domain, for example.

Now five or six years ago, that -- it wasn't even an option. I think that thinking has evolved over time as to whether or not an open informed consent is a valid way to go. And I think we're seeing some debate as to whether or not -- I think it may be swinging back a little bit because when we talk about informed, there's a question as to whether or not you could possibly be informed for future events, and these are issues

that you're more than familiar with.

But the decision was made to make the most of the investment, to go for an open informed consent which would allow all scientifically valid questions related to disease and biology to be investigated by VA credentialed researchers, all within the secure firewall, if I could use the term, of Department of Veterans Affairs.

DR. GUTMANN: Nelson?

DR. MICHAEL: The question is to Greg Biggers. Now as we move away from maybe a paternalistic historical system of research where, you know, the physician-scientist knew best and we described research volunteers as you say, as initially unwitting participants and you would give us that evolution --

MR. BIGGERS: Well in fact, I meant that as a spectrum, not necessarily an evolution.

DR. MICHAEL: Yeah. So I guess my question is -- and you know, all of us have seen this if you sit in a meeting. Usually there are one or two people that are dominant and they can completely change the tenor of a conversation, the rest of the people, depending on the time of day and cortisol levels sometimes will just go along with those relatively dominant voices.

And I just -- I'm really just intrigued by this framework. How do you -- how do you negotiate the potential dilemma? You're basically trading one paternalistic environment for simply one where you distribute the paternalism a bit. In other words, you have a community of research participants, some fraction of them are going to naturally be more engaged, naturally going to be more invested in the process, and may, in fact, be bringing along the rest of that community in a way that isn't necessarily an open deliberation, but one that has a less distributed execution of

stewardship.

MR. BIGGERS: Right. So that's a very nuanced question to me, and I'm trying to think how to deliver a nuanced answer briefly.

So I think -- let's be careful not to assume that engaging more people in decision-making automatically distributes paternalism to more people. But yes, there are new challenges, if you say we are going to take a more distributed approach to decision making and things like that.

And we're seeing a spectrum of governance approaches. Often a group of people will kind of designate quite a significant proxy for decision-making to some kind of council whom they think represents them. And in fact, that is the case of PXE International and many of those other groups like that. Those people don't necessarily want to be contacted every time there's a research opportunity.

And then -- so you have that, that's kind of a dominant form. But as more and more people are connected to the internet in a frequently transactional manner, you know, and as we're entering a world where more people have smart phones than have access to healthcare, it is becoming much more feasible to send out opportunities for people to weigh in on decisions about what they would like their tissue and data to participate in as it pertains to research.

DR. GUTMANN: Barbara?

DR. ATKINSON: Yes. I'm interested in, Leonard, hearing a little more about the overlap and similarities and differences between the quality improvement piece and the research piece. And I'm interested in it because I think a lot of us in this country are having an issue with downloading EMR data into research databases and then who owns it.

Oh, sorry, forgot. Downloading the research -- EMR into research databases, who owns it? And really very different controls on the quality assurance piece versus the research database piece. So in the VA, since it's all one system, I'm not sure you have necessarily as much tension between those two things as when a hospital sort of owns the EMR and the researchers, if you will, own the research database.

DR. D'AVOLIO: I don't think that it's an institution specific issue, and we're certainly not immune to it within the VA. We have two silos, as everyone suffers from. And in fact, the reason the CTSA's were created under the vision of Dr. Zerhouni, was to try to tear down this wall and to speed the translation of science. There are controls that were put in place some time ago for very good reason to protect research in very different ways that operations is governed. And the VA certainly abides by those controls with IRBs and the rest of it.

You'll notice I used the word "learning" several times and not the word "research." The sad truth is, if you talk to a practicing clinician about whether or not they'd like to participate in some kind of research, this is more often than not a hassle. They are very busy people and they are taking care of patients. And research means engaged in research, and that simple term means that they have to log on to a web site and spend several hours completing credentialing forms. And people are nodding because they probably have had to go through it in their own institutions.

So on the other side of the fence is operations. Where if I simply change a formulary, which I need maybe a group smaller than this in order to do, I can have dramatic effects on what is ordered and how often. But I don't learn from that. And in fact, if I attempted to, through a non-biased approach such as randomization, I now jump that fence. And I'm not sure where that line is. Is it an attempt to learn? That

would be a shame. Is it an attempt to publish? I guess I don't know where the line is anymore.

And I think that with point of care research, we are very intentionally blurring that line. And I think that the healthcare system needs to take this up and soon, because we're not going to be able to answer every question with a clinical trial. And observational studies, while it's a tool and it has terrific pros, but some heavy cons as well.

So we have those issues. The VA has -- locally thus far has been great in understanding that this is research but it has great quality improvement potential. But I think we've only taken the first step, and it's going to be a lot of fun to see what happens as we continue the debate with -- we have a panel of ethicists that we're working with from outside the VA as well as with the focus groups, as we push this forward and try to find where that line is. Because there's heavy cost to calling it research.

DR. GUTMANN: Just so we understand, when you said the VA has been great and it understands this is research, this is a case where having genomic data does make a difference. It makes -- because of the quantitative difference, it also makes a qualitative difference. That is, when you're doing clinical research on subjects, you need to spend a lot of time and there are a lot of confounding variables. So you can't even approach what a really good research study would be.

But if you -- if the VA succeeds in getting anywhere close, they don't need a million. I mean, when you get tens of thousands, you get a database and you can start doing -- and I'll put it in quotes -- but "research" with this blanket consent, then --

DR. D'AVOLIO: Let me draw a pretty thick line between the two projects --

DR. GUTMANN: Okay.

DR. D'AVOLIO: -- and say that the Million Veteran Program is a cohort building initiative to do genomic discovery with the intent of supporting personalized medicine. And so we'll see how far down the road. I mean --

DR. GUTMANN: Okay.

DR. D'AVOLIO: -- there's been some debate as to whether or not there's a lot of value in genomics alone. I think that Nobel Laureate biologist Sidney Brenner was asked, what's the predictive value of genomics? And he said, well, you know, astronomy took an interesting turn back in the day, too. It became astrology and astronomy and genomics might be genology at this point.

DR. GUTMANN: Fair enough. But you still have a big database.

DR. D'AVOLIO: An enormous database.

DR. GUTMANN: And blanket consent to use that for any research within the VA?

DR. D'AVOLIO: Blanket consent. So there is -- yes, it's a --

DR. GUTMANN: I'm not saying that badly. I mean --

DR. D'AVOLIO: No, I just have to be careful about it, because I believe that the wording -- it has to be related to biological discovery related research as well, and others could speak to the exact verbiage. But I do want to just clarify that MBP is one thing. But the VA has -- every healthcare system has an enormous database of research that could be used to understand what's happening and how to improve care.

The point of care research program is starting with a pretty basic clinical effectiveness or comparative effectiveness question. But I do think -- and the reason I included this is because there's a huge problem in biomarker validation right now, and

that's a very genomics related topic.

See pharmaceutical intervention is a new blockbuster drug is worth \$80 million in seven years to bring to market. That may not be the case for a biomarker, which has a one-time use. And the FDA is struggling with how do we validate biomarkers? Do we run large-scale clinical trials?

Well, what if you could do something like a point of care clinical trial? So you could validate the effectiveness of the biomarker. It's certainly not a tool for appropriate interventions, where you do need to control the data more carefully and have a whole 'nother -- it's a very good reason to do phase three clinical trials outside of healthcare.

But in any case, there are different tools for the job. And I think what we're missing right now are tools that can fill that gap between observational and an RCT.

DR. GUTMANN: Steve. And I will -- that will be the last question. We'll wrap -- Anita, did you have -- Steve and Anita, and then we'll wrap up.

DR. HAUSER: Thank you. Lawrence, for the Million Veteran Initiative, has a decision been made as to when or if to share this genomic or other deep data with the participants?

DR. D'AVOLIO: Yeah. That's a very interesting question which I'm never able to dodge at meetings like this.

(Laughter.)

DR. D'AVOLIO: So yes, the decision has been made right now that that information will not be shared. Now I'd like to point you to that paper back in 2002 where the VA's first biobank, the first DNA bank, they used a model in which the data

in the case of an emergent finding, it will go to a panel whose job it is to decide whether or not it's actionable and that information should be shared with patients. That was done under a clinical trial model where each clinical trial had an infrastructure to be able to deliver that information back.

Now I'm not in a position to be able to speak to the logic or the long-term decisions about the current policy. On a personal level, I believe that there may be a difference between what you do to launch a large-scale program today versus how this will evolve over time. And I think that we need to -- I know that people are preparing to deliver that information. But the current policy is that it is not shared.

DR. GUTMANN: That's a good clarification. Anita?

DR. ALLEN: It's a quick question. So you have, at the VA, a kind of semi-captive audience in terms of your patient population, right? Many of these gentlemen and ladies cannot afford to seek healthcare elsewhere. You also have the ethos, the culture of the military, which is one of cooperation and obedience. And I'm wondering if you've given some thought to how those two things may bear on your ability to so successfully enroll people in your program?

DR. D'AVOLIO: Yes. Yeah, veterans do historically participate much more readily in research for the reasons that you just outlined. I think that, you know, your average response rate to a survey is probably under seven percent in the general populace, and that after two attempts to contact we're seeing close to a 19 percent response rate from the veterans.

I think that it's an incredible credit to the veteran population for wanting to continue to serve and we're very appreciative of that. And where -- I think it's safe to say we're probably even more protective as a result of that in general. This is just

research in general and not anyone's specific position. But that within the VA, we do recognize that, because there is not just the culture of giving, but potentially the culture of captive audience and what ethical implications that may have, that we have to be especially considerate of truly informed consent and how we handle that veteran's contribution.

DR. GUTMANN: Thank you. We're going to continue with our roundtable. So but before we do, thank you Leonard, thank you Greg, very, very much.