ROBERT GREEN INTERVIEW PART TWO - INTRO

Hello again, Ars Technica readers. This is the second installment of a three-part interview with medical geneticist Robert Green on the subject of personal genomics. Or, the fraught question of whether you should boldly have your full genome sequenced, and thereby expose yourself to iron facts about your heritage and vulnerabilities that could be written there.

If you haven't yet heard part one, there's a link on the page where this player's embedded, and I strongly suggest that you go back and listen to it before this one.

And with that - back to my conversation with Robert Green.

TRANSITION MUSIC

Robert Green: So imagine you have a library, and it's got thousands of bookshelves and we pull out one book, your book for example, 527 pages of letters, and there is a single misspelling somewhere in there, and your job is to say, "Does that ruin the book or not, does that single typo ruin the book or not"?

Rob Reid: A fabulous moment, I saw Craig Venter speak once and of course he is one of the fathers of the field of genomic science, the people who're putting on the conference, is a cool visual and I think that Craig wasn't expecting this, so it was a cool thing for him as well. They printed his entire genome, 'cause he was the first human being to have his genome sequenced, correct?

Robert Green: Mm-hmm (affirmative).

Rob Reid: And they printed it up and it was hundreds of very large hardcover books, and they carted it out on the stage, and just that visual of what three billion letters looks, and like that just seeps into your head of like, "Wow, hard to find the typo".

Robert Green: Yeah.

Rob Reid: But the immensity of that is really quite something. Now tell me this, you were not yet involved in genomics when the human genome project was wrapping up.

Robert Green: That's right, I was a neurologist and came to genomics sort of later in my career.

Rob Reid: Let's talk about that story because that does touch on some of what we're talking about, and it's also just a fascinating personal story.

Robert Green: Well thanks, I was a neurologist for the first half of my career, and I was studying Alzheimer's disease. And I was running clinical trials in Alzheimer's disease, really your classic randomized clinical trials, one after another, after

another, and of course it's been very frustrating because for the most part those clinical trials have not proven that any medication actually changes the course, or prevents Alzheimer's disease yet. But in the course of that I started working with a colleague, Lindsay Farrer at Boston University on the heritability of Alzheimer's disease.

Because when I really started this, it wasn't at all clear that Alzheimer's disease had anything to do with genetics, and gradually it has dawned on us through a series of epidemiologic studies and other types of studies that it too is a genetic disease. Now the genetics aren't straightforward like Huntington's or cystic fibrosis which we've been talking about, it is one of those common complex diseases.

Rob Reid: Polygenic, right?

Robert Green: That's right, that has multiple genes responsible. Just because you have a parent who has it doesn't mean you're going to get it. We clearly demonstrated in the early days of these EPI studies, your risk was higher if you had a first-degree relative. Your risk was even higher if you had two first-degree relatives, and so forth. So we were able to start demonstrating that, then we were part of large-scale studies that actually found many of the polygenic genes responsible for Alzheimer's disease. And in the course of all this, the number one gene that was early found to be a risk gene for Alzheimer's disease was a gene called APOE.

Then I went naively to a geneticist at my institution and I said, "Hey some of my families are interested in learning about their APOE risk, 'cause they read about this in newspaper. Is it okay if we test it and give it to them?", and they said, "Oh my God, no way under no circumstances can you do this, that would be completely unethical, inappropriate!", and I said, "Why?", they said, "Because, well they would be distressed, they would believe they were gonna to get the disease. You would be doing them a huge, huge disservice. You would be causing harm".

Rob Reid: Because there's nothing we can do about it. And how much does the bad configuration of APOE increase one's risk of Alzheimer's?

Robert Green: Well, quite a bit. If you carry one copy of it you might be at two or three times the population risk.

Rob Reid: Mm-hmm (affirmative).

Robert Green: If you carry two copies of it you might be at eight or ten times the population risk.

Rob Reid: Now this is very interesting to me, because I actually have a personal experience with this. I started getting high cholesterol, not terribly high but high enough that you're concerned. And I ended up going to a research cardiologist at UCSF

who was miraculously covered by my insurance, and the deal was that you get access to this world-class cardiologist, but your anonymized data would be part of his research, which seemed like a fair deal. And when he took my blood he said, "Okay we're going to do a very sophisticated lipid panel, look at your blood, and as part of that we're gonna find out about a few other things including this APOE thing".

And he said, "But I can't, and will not tell you the results of that test, and I'm telling you now before you get the test, so you won't think I saw something horrible that I'm keeping from you. I have no idea what the test is going to say, the test is gonna come back, we're going to know your APOE status and we, will, not tell you, period. Because we at UCSF, one of the best medical schools on earth, have determined it would be unethical to tell you this. So don't even ask. We are not telling you this".

Robert Green: Right, and that is because they felt that learning this was going to terrorize you.

Rob Reid: Mm-hmm (affirmative)

Robert Green: And this was the prevailing view, being a little bit contrarian and also, having a background in clinical trials I said, "Really? Can you show me the proof of that"? And they pointed to Huntington's disease, and pointed to other terrifying diseases and the trauma that people felt.

Rob Reid: They pointed to the deterministic narrative.

Robert Green: Exactly, and I said, "But this is different, this is a probabilistic piece of information". You might get it and your risk is higher, but you also might not.

Rob Reid: Mm-hmm (affirmative).

Robert Green: And they said, "It doesn't matter, people won't understand", and what I did at the time was fairly unprecedented. I actually treated information as if it was a pill, and then I did a randomized trial with a kind of placebo. And so we took people and randomized them into one arm that learned their APOE status, like you couldn't do with your lipid panel, and another arm that did not learn theirs. And then we simply tracked through what happened to those people in every conceivable, highly validated measure of distress and depression and anxiety. What they understood, what they got wrong, what they did with the information and so forth. Who they told, all these interesting issues.

We've done now, four such randomized trials, looking at it from all different angles, and the bottom line is that when people want to know, when they raise their hand and they say, "Yes, please tell me", they actually do pretty well.

Rob Reid: You basically checked their general level of mental health, stress, coping abilities and so forth during the period leading up to them finding out.

Robert Green: Mm-hmm (affirmative).

Rob Reid: And then you carefully tracked them for many months after they found out.

Robert Green: Mm-hmm (affirmative).

Rob Reid: Some people elected to find out, some did not, and you didn't find any significant change in the distress level of those who had said, "Yes, tell me this information."

Robert Green: That's right now, we saw signals. I mean, it's definitely upsetting for some people when they learn this.

Rob Reid: Of course.

Robert Green: We could see that upset, and then we could see them return to normal levels. And so, I don't want to be cavalier about this because there are definitely rare instances where someone says, "Yes, I want to know", and they miscalculated the impact that this information was going to have on them. We've seen that now with some of the direct consumer genetic company customers who quickly checked the yes box, learned something and then kind of wish they hadn't. But for the most part in general, and really for the vast majority of people, if they make that calculation that they want to learn it, inherent in that calculation is a self assessment of their ability to manage and understand the information.

And they make that very quickly, sometimes instinctively, but they make it very accurately for themselves. So, this is a key component, you're not forcing this information on people, but when you give them an honest choice, would you like it or would you not, they tend to choose very quickly and very accurately.

Rob Reid: And this was the first time that anybody had researched the question of how do people deal with ambiguity in their genetic makeup, correct?

Robert Green: There's certainly has been a lot of people writing about it, and a lot of case reports. But I do think it was the first time anybody had dealt with it in this kind of rigorous, methodological way.

Rob Reid: Funded by the National Institute of Health, this was a major, major study that you did. This wasn't just a couple people pass through your office. It was a massive study, right?

Robert Green: It wasn't massive in terms of numbers but it was massive in terms of inertia.

Rob Reid: Mm-hmm (affirmative).

Robert Green: Because there were quite a few people in the community, the kind of people who review your grants, the kind of people who review your papers, the kind of

people who stand up at conferences and tell you that what you're doing is absolutely wrong. There were quite a few people like that who felt that this was absolutely inappropriate.

Rob Reid: To even look into this?

Robert Green: Really, to be even walking down this path.

Rob Reid: And what is fascinating about that. We are literally going to go through a see change. There will be a before this happened, and an after this happened period in human history, where people go from pure ignorance about this radically important information. Everybody knows nothing about it, because it costs three billion dollars and takes 13 years, to a future of, what would you say it is, 10, 15, 20 years? It's going to become something that you will have to go out of your way not to know, because today it costs about a thousand dollars to get your genome read. Very few people are going to do that for fun, particularly in light of all this ambiguity.

Insurance isn't paying for it, doctors aren't urging it, but there is gonna to be this pivot point, because we've come from three billion dollars to a thousand dollars, it will be practically free in a short number of years. When do you think we get to the point where you kind of have to go out of your way not to get this done. Is that a decade off?

Robert Green: I don't think it's quite as soon as a decade, but it's definitely coming, and it's going to become free.

Rob Reid: Yeah.

Robert Green: You're absolutely right. This technology is moving so quickly, and there are so many spinoffs from the genome. So many opportunities to leverage it for research investment, for product marketing, for novelty. The genome itself will probably be a loss leader, for most people.

Rob Reid: Yeah.

Robert Green: So I do think it's going to get to free. And remember that this early research was coming out, we were doing this between 2000 and 2005, the very first few steps in this. Little did we know, over in Silicon Valley, and around the world there were three companies planning to launch direct to consumer genetics. All three of them launched in 2007.

Rob Reid: Right after, or tight as you were doing this?

Robert Green: Right as we were publishing.

Rob Reid: Publishing, yeah.

Robert Green: Publishing paper after paper about how-

Rob Reid: That's when 23andMe-

Robert Green: That's right.

Rob Reid: ... and Navigenics, and what was the third one?

Robert Green: Decode me.

Rob Reid: Decode me, yeah.

Robert Green: What happened was, people started to get wind that these companies were going to launch with this direct to consumer. I believe that all three of them, at least two of them, but I believe all three of them initially provided APOE. And it was a lightning rod for the criticism of these companies. It's obviously not the only thing they provided.

Rob Reid: I got my APOE information from 23andMe shortly after it happened because I was so damn interested after this UCSF thing.

Robert Green: And you're clearly among the information seekers-

Rob Reid: Yeah.

Robert Green: ... who would want such information.

Rob Reid: What happened is, just by good luck, our research got noticed by a lot more people, because APOE was part of the lightning rod of criticism for these companies. And our evidence was the only evidence that was saying, "Hey you know what, maybe it's not so scary, maybe it's not so damaging, maybe it's not so destructive and toxic to provide people who want it-

Robert Green: Yeah.

Rob Reid: ... with this information.

Robert Green: And now you have since done at least two more, much deeper studies that are about whole genome sequencing. So you are looking again, looking at the near future and what a very high percentage of us are going to be dealing with psychologically soon and for the rest of our lives, so you have taken small-ish, but not insignificant subsets of people, and have given them the treatment that will be standard care in 10 or 15 years. You've given them their whole genome. You've done this for adults, and now you are doing this for babies.

Rob Reid: Yes.

Robert Green: Let's talk about that research and what you are starting to find, because the consequence is fascinating to me. It is literally taking people and putting them in the very near future that billions of us are going to have to occupy.

Rob Reid: The three questions that keep getting asked, in every step of progress along the way in the sort of genomic journey that our society's on are these, "Is the information itself toxic, will patients and providers completely misunderstand and do bad things based on the information"?

Robert Green: So you mean literally toxic?

Rob Reid: Literally toxic.

Robert Green: By telling you this?

Rob Reid: By just telling you this.

Robert Green: Yeah.

Rob Reid: Would you live your life, basically the equation that your lipid doctor. Their conclusion was, they would do you harm. Now, they base that on anecdotes and custom rather than evidence.

Robert Green: And in the detail end of the deterministic era which had shaped everybody's psychology, particularly for a cardiologist, he was not a genomic scientist, he was a cardiologist, and he was more in the periphery of this and so, his psychology have been shaped by the same determining.

Rob Reid: Yeah, and he probably gone to either a geneticist or his institutional review board, and they had all with one chorus of voices said, "Absolutely not, you will be doing harm to people". Because there were five reputable papers and journals like Science and Nature that had been written by the world experts that said, "Under no circumstances should people be returning APOE", that's how ingrained this was. By the way, the third question that always gets asked is, "Are the benefits to your health going to outweigh the harms and the costs"?

Robert Green: The Lynch syndrome like situations, where having done this you could save your life and that of your loved ones.

Rob Reid: Yeah, or just improve it, yeah, inform it, or in other words that totality of the benefit, the totality of the potential harm and let's face it, the cost, those are the three questions that were asked about APOE at the very beginning, and they're the same three questions that are being asked now about the entire genome. But it's a much harder question to answer experimentally, because the genome isn't one piece of information, the genome is a series of probabilistic pieces of information whose value get an amortized over your entire lifetime, and whose risks get amortized over your entire lifetime. And so, the way to do

this if you were really good at designing experiment, and I'm sure you'd like to volunteer any future children that you have, is enroll a million newborn kids at birth, provide their genome to their parents and all of their doctors, direct their health care with genomic input for their entire lives.

That's you know, avoiding certain medications and foods, that's helping them get to reproduction with the advantage of all this information, that's hoping them customize their diet and exercise in their 20s and 30s, that's helping them avoid cancer in their 40s and 50s, thinking about how to avoid Alzheimer's disease when they're older, and then checking to see if you've caused them benefit or harm at the end of their life.

Robert Green: So, that would be a pretty quick study.

Rob Reid: Yeah.

Robert Green: Yeah, that would make the movie Boyhood look like a very, very ambitious project. We would start reaping the benefits from it in 75 to 100 years, so that's hard obviously, that's hard. So, what are you doing instead?

Rob Reid: So what we did in the MedSeek project is a very, very abbreviated start to that. Keep in mind that nobody had really tried to take healthy people and systematically try to figure out a way to give them their information back. I mean, it's stuff that's being done in an ad hoc way by certain one off doctors, and concierge doctors, and certain research projects. But nobody had systematically said, "Okay, here's your entire genome, and here's what I'm gonna tell you and your doctors about it", made a decision about what stuff to return, and what's not to return, and then templated the whole prospect, actually modeled the whole prospects.

Robert Green: In this particular study, we're talking about the ones you did with adults at this point?

Rob Reid: Yes.

Robert Green: Yes.

Rob Reid: The adult MedSeek Project we called it, is that we designed such a study, and it took us years to even design it. The MedSeek project basically said first, "How many genes are we gonna look at"? Remember, there is potentially five to eight thousand, we decided to cast a broad net. Remember that many panels right now that purport to screen your entire genome are looking at a hundred genes, so we looked at close to five thousand. Number two, we said, "How do we report it in a way that any doctor can understand the information and use it?", we created a one page report.

Think about that, five thousand genes, all sorts of categories we've been talking about, dominant, recessive, pharmacogenomics, and some other things, we put on a one page report for a doctor. 'Cause you know what? They don't wanna learn the discipline of genomics, they just wanna know what's useful to their patient.

Robert Green: And these are primary care doctors?

Rob Reid: Primary care doctors.

Robert Green: This is their family doctor, their internist, the person they go to first when they have a sniffle or they're not sure what's going on, so these are not geneticists or genetic counselors, these are the people who will be dealing with this information for hundreds of millions of us real soon now.

Rob Reid: And it sounds absurd when you think about it, 'cause genomics is so complicated, you need your specialist. But look, primary care doctors interpret x-rays without being nuclear physicists, they interpret chemistry reports without being chemists, it's really a matter of packaging this and directing them with sufficient clinical support that if they get confused they have somebody to turn to. That's a kind of heretical idea honestly, we have said, "Genetics is so complicated and so scary, only the geneticists should hold onto it", it doesn't make me very popular among many of my confreres in genetics because what I'm saying is, "You know what guys, this is too big for our small specialty, this is something that every doctor's gonna have to deal with".

So we created a one page report, and then we didn't just throw it out there, we put all sorts of safety nets in place. This taping reminds me, we audio taped every interaction between that primary care doctor and that patient, and we transcribed it, and we examined it for errors. We followed their electronic health record in real time to make sure they weren't even ordering something inappropriate.

Robert Green: Ordering a medicine that might interact poorly with their genes?

Rob Reid: Yeah, or, we didn't really expect this, but the fear here in extreme cases is that cardiology example. So, a primary care doctor says, "Oh my God you have a long QT variant, let's get you over to the surgeon for an implantable pacemaker".

Robert Green: Right, so you kept an eye on those crazy outcomes?

Rob Reid: Yeah, we didn't really expect that, but out of a lot of careful safety concerns, we wanted to be able to track everything that was being done. We worked with our colleague Heidi Ream in the Laboratory for Molecular Medicine to get a really standardized way of interpreting the variants that we could defend, and publish, and say, "This is how we got to those many variants". Then, we circled back around when we would find something, and we would re-examine the patient,

what's called deep pheno typing. So, we'd find an unanticipated variant for some crazy rare genetic disease, you know, punctata albescens, which is Latin for white spots in your eyes.

Robert Green: Sounds much better in Latin.

Rob Reid: I know, it always does.

Robert Green: 'Cause if the doctor said, "Dude, you've got white spots in your eyes", I'd be, "I'm paying you for this"?

Rob Reid: And the patient says, "Hey, you know that's funny because I don't have very good night vision", that's not a life-threatening disease but all of a sudden it's an explanation or something that nobody had ever explained, and we started finding several examples for that. So, the final surprise was just even among the first hundred people who were sequenced, the first hundred adults, it turned out that 15 or 20 of them, depending on how you cut the threshold were carrying a dominant, or biolytic, meaning two copies of the recessive risk variants, so they should've had disease if it was 100% penetrant, and of course they didn't all.

Robert Green: Right.

Rob Reid: But more than a few had some fragment of the disease, some unsuspected fragment that had never been identified as genetic. So what this study says is a couple things, it says first of all, it's possible to do a rigorous trial wherein you give people all of the information in their genome, a lot of people have just basically thrown up their hands and said, "That's not possible", number two, it's possible to work through primary care doctors, many people have said, "Don't you dare work through primary care doctors".

Robert Green: Which we are going to have to do because everybody's going to get this information whether we want them to or not, and they are going to their doctor with that.

Rob Reid: Yeah. Number three, it says all this rare disease is rare individually, but when you look at a lot of genes, which we were the first to do, amazingly we are the first ones to look at nearly five thousand genes in anybody whom we gave the information back to. When you look at that many genes, you find that collectively genomic diseases are common.

Robert Green: How common?

Rob Reid: 15% to 20%.

Robert Green: So 15% to 20% you would infer of the general population, is actually caring a genetic disease that could well influence them, we're not talking about a time

bombs like cystic fibrosis as a rescissory, but something that could affect them, one in five of us roughly have got that, don't know it, and may well benefit from the information, or in horrible cases, may well freak out because there's nothing we can do. But it's one in five?

Rob Reid: Exactly, although I wouldn't call it the disease, they have a genetic variant that could the predisposing them to the disease.

Robert Green: Right. Or give them fragments of it like this night vision thing that you described. And it's just fascinating to think how much more we will know about this five, ten, fifteen years from now when it's not hundreds but, tens of millions of people who've been through this, if it's done in a rigorous way.

Rob Reid: Right, and remember our research infrastructure is not really set up to follow people for years.

Robert Green: Right.

Rob Reid: I mean, the grant cycle that I get is three year grants.

Robert Green: Yeah.

Rob Reid: And, if I'm really lucky I get a five-year grant.

Robert Green: Right.

Rob Reid: But we looked within the Framingham Heart Study, and the Jackson Heart Study, at a few people that had been followed for decades.

Robert Green: Yes.

Rob Reid: And again, very small sample sizes. But if you follow people for decades, these fragments start appearing more and more.

Robert Green: More and more.

Rob Reid: And in the Framingham group, there were only five people who carried this particular set of mutations we looked at, but four out of five of them had actually developed a significant fragment of the condition by those 20 years. Even our concept of penetrance, the probability that you were gonna get the disease, is limited by the time window within which we judge that.

Robert Green: Which is usually three years max.

Rob Reid: Yeah.

Robert Green: So things that seem like they are 5%, or 10% penetrant, may actually have much higher penetrance.

Rob Reid: Yes, 'cause if we follow them long enough, which is inconvenient for all our research careers-

Robert Green: And expensive, and probably impossible in a lot of cases.

Rob Reid: If we follow them long enough, we might just find out that they are a lot more penetrant than we realized.

Robert Green: And what a incredibly important thing for society to know that, "Whoa, look at all these high penetrant things that we never even knew about". Now, I don't know if this was a formal and the point of the study, if it wasn't you have a very strong intuitive sense of whether the costs or benefits of knowing one's whole genome, in this relatively primitive time of 2017, or even earlier when you were doing the work, when we're far more ignorant than we will send be about what all this data means. Which you say that for the most part for most people, finding that information out the benefit outweighs the cost, or vice versa?

Rob Reid: Cost is a really important part of this equation, because one of the arguments that's been put forward against the entire genomic revolution is, "You're gonna give people a whole lot of probabilistic information, they're gonna go out in crazy uncontrolled ways, pester their doctors, or their doctors out of caution are going to order all sorts of tests. You're gonna drive up the cost of healthcare without any tangible benefits".

Robert Green: And also, take resources which are finite away from people who might genuinely be sick, and I think the term you used, I wrote this down 'cause I thought it was so elegant, "Robbing the medical commons", yeah.

Rob Reid: And that's a term my colleagues Wylie Burke and Amy Maguire have used to indicate that exact concept that, "Look, as a society we've got a pool of resources, let's not waste it on all this fanciful, predictive, probabilistic, indulgent information when we don't really know if it's gonna come true, or if our intervention is gonna help.

Robert Green: And then they might stampede the clinics and then all of a sudden people who have actually developed the 2% penetrant condition can't get an appointment for eight months because the worried well are filling the lobbies and spilling out into the neighboring Starbucks.

Rob Reid: You paint a great picture, and it's also really a social justice issue and they have a great point it's the people of means who can afford right now to get this, it's the people of means whose doctors are going to indulge them and it's just taking focus away from the tremendous public health issues around obesity and

smoking and proper nutrition, which we absolutely know will make huge differences in health outcomes. Why are you paying so much attention to this?

Robert Green: Yeah. Because I've seen about your Genome and taking proactive steps, let's face it, would be a very expensive hobby. It's not in the budgets of most normal people. So, that is a really important social externality, I'm very glad that we hit on it. But let's again go back to that notional person, who isn't necessarily greedy or evil or selfish. It's not Mr. Burns from the Simpsons, it's somebody who has enough means to be able to afford a test, and afford tests for their families. It's somebody who says, "I love my children, I love my family, I want to do what's right for them because I'm in a position to do what's right for them". For that person, would you say, on the balance of things, for most people the benefits outweigh the costs in 2017, 2018? Or vice versa? Or is it just impossible to say?

Rob Reid: Honestly, we would tell that person, we don't know. If they are curious, they are an information seeker, they want to be on the cutting edge, want to learn about this, I would say, "Educate yourself about the deficiencies of the testing, and the limitations of it, if that's something you want to pursue, I wholly support that". Because I do believe people have a right to information about themselves, I don't think we should be regulating information, particularly about you. But, I do think there's a responsibility we have, to be very clear about what's standard of care, and what's not standard of care.

And sometimes, again, particularly among my Silicon Valley friends, who seem to be living in the future half the time, if not all of the time, in their minds, this is already a done deal. And he's like, "Of course, we're all gonna get sequenced, and we're all gonna benefit, and we're all gonna prevent every disease that human beings are plagued with". We're not quite there yet.

Robert Green: But only that first statement is true-ish. We are all going to get sequenced at some point. But whether we're all going to benefit and whether we can afford the cost of dealing with that information, that is yet to be seen. Let's talk about BabySeq now. Tell us about what that project is.

Rob Reid: So, it's one thing to sequence adults. They can choose or not choose as we said, to sort of have this experience. And of course by definition, since you don't hold a gun to anybody's head, all of the people who're adults, were interested enough to come into the study. But people have argued, even Francis Collins has talked about a day when all human beings will get sequenced, or perhaps have other types of OMIX screening at birth in order to prepare their parents and their families and their providers with the information in the book of life.

Robert Green: And there is a significant precedents for that because the states mandate a lot of testing for newborns already, right?

Rob Reid: That's right. Every developed country has a newborn screening protocol, whereby a little prick of the heel is taken and some biochemical testing is done, ironically, for a number of genetic diseases.

Robert Green: And blood chemistry and other things like that, and making sure they don't live with infectious diseases and so forth, right?

Rob Reid: That's right. And so there is a limited number of tests, and there's a whole discipline around this, "Which tests belong on that screening panel, which don't". There's all whole politics and discipline around that component. But the question arises, "Now that you've got this technology", and genetics arguably influences children's lives even more than adults.

Robert Green: Mm-hmm (affirmative).

Rob Reid: Because there are a awful lot of childhood genetic conditions. "Should we be considering the notion of sequencing newborns"? Maybe starting with the newborns who're really sick. Maybe the ones that are in the neonatal intensive care unit who don't have a diagnosis. And so the national genome Institute and the national Child Institute both institutes at NIH, collaborated to put together a set of proposals, and ours was one of those. And our proposal, which we nicknamed the BabySeq project.

Robert Green: Seq being like sequencing, not like we're looking for babies.

Rob Reid: No.

Robert Green: S-E-Q.

Rob Reid: S-E-Q.

Robert Green: Yeah.

Rob Reid: Actually enrolls families in a project where we randomize the family, again to receive exome sequencing, or not to receive it. And we've done that for a series of families in the neonatal intensive care unit and for a series of healthy babies. The ones in the neonatal intensive care unit, that's not really big news, that's been going on for a few years. The part of the project that's really controversial is the healthy infants. And it's controversial for a couple of reasons, number one, all the reasons we've talked about. The ambiguity, the uncertainty, the question that, "Will these parents pursue some diagnostic procedures, or even surgeries that isn't warranted"?

Robert Green: Well, I guess you can always ask the baby what it wants.

Rob Reid: But that's the other reason it's controversial.

Robert Green: Yes.

Rob Reid: Because the babies can't give their own permission. We're even identifying a few adult onset conditions in these babies.

Robert Green: Wow. So you're saying this baby is fated to experience this condition at age X.

Rob Reid: 20, 30, 40-

Robert Green: Wow.

Rob Reid: Not just, yeah.

Robert Green: Yeah.

Rob Reid: And there's been a strong tradition in genetics where you do not return genomic information about an adult onset condition to a child's family, you wait. And the expectations-

Robert Green: You don't even tell the family.

Rob Reid: You don't even tell the family, because-

Robert Green: It'll happen after they're 18, after they've achieve their majority.

Rob Reid: So the idea is that after that infant, or child, or adolescent grows up, they can elect for themselves whether to learn that. The right not to know is enshrined in genomic science. There's a real controversy in my mind about how much we should respect the right not to know, versus how much we should be telling people when they're at risk.

Robert Green: And particularly we can imagine a scenario in which a baby gets their genome sequenced at birth, and low and behold they are prone to diabetes, and if they start taking steps, if their parents start taking steps, early in life, making sure that their exercise, kind of guiding the development of their palette. There's all kinds of proactive steps that might be taken about a condition that won't onset until age 30, or 40, or 50, that if you withhold that information, the parents can't be looking after the child in a way that foresees that. Plus the fact that, it's not like at 18 you suddenly become worldly wise and like, "All right, you're 18 kid, guess what, there's some really scary stuff in this envelope. Wanna read it?"

Rob Reid: Yes.

Robert Green: I don't know if I want that to happen during my freshman year.

Rob Reid: Exactly.

Robert Green: Yeah.

Rob Reid: But there's even more salient questions. We had one baby in whom we found a BRCA2 mutation, and at that time, our protocol did not allow us to inform the family because we were not at that time reporting any adult onset conditions.

Robert Green: Yeah.

Rob Reid: We had saliva from the mother and father and we were able to check, in fact the mother was-

PART 2 OF 3 ENDS [01:06:04]

Robert Green: We had saliva from the mother and father, and we were able to check, in fact, the mother was carrying it.

Rob Reid: The mother was carrying it. Now we're bumping into her right to not know.

Robert Green: Exactly. Now we have a real moral conundrum. None of us were comfortable saying, "We know this baby has BRCA2, and we can't tell the family," and more than that, we know it's come from the mother, and she's carrying it, and she doesn't know.

Rob Reid: And she's sitting across from me right now.

Robert Green: She's sitting across from the table from you. How do you solve that? Well, it may not seem particularly heroic, but we paused our study for three months, we re-negotiated with our partner's healthcare institution. It was U-Board that sort of monitors the safety of our research. We re-negotiated with the FDA, who had taken a special interest in our research, and were following us quite closely. We changed our protocol so that we could take a subset of adult onset conditions and return them to the family. We called that mother back in after we'd done that and held our breaths while we said to her ... They wouldn't even let us say, "You have something." First we had to ask this question. "We sometimes discover things in the baby that may be relevant to the other family members."

Rob Reid: And their health.

Robert Green: Right, "Would you like to know?"

Rob Reid: In such a hypothetical, "Would you want to know?"

Robert Green: Right.

Rob Reid: Yes.

Robert Green: Held our breath in case she was having a bad day and just said, "No, no, I don't want to know that." Fortunately, she said yes.

Rob Reid: Yeah.

Robert Green: Then we were able to offer her that information. You know what the first words out of her mouth was? "Oh, that explains it." It turns out that unbeknownst to us, and we'd taken a very detailed family history, unbeknownst to us, there were four or five distant family members who had breast and ovarian cancer. We had missed them on the family history. This teaches us a lesson. The family history is not perfect. Half of the breast cancer cases that are BRCA positive actually have no family history of breast cancer. Family history is an important entrée into genetic risk, but it's not the only entrée into it.

Rob Reid: Particularly for an adopted person like me. Now again, I know I kind of keep bringing up this theme, but you did something that might become a universal thing fairly soon, sequence the genome of a newborn. You found this awkward fact, and you were able to confer for three months with the FDA, the brilliant people at Brigham and Women's, and Broad, and Harvard, and MIT, and the whole nine and come up with this very careful solution most pediatricians who have hundreds and hundreds of children coming through their practice every year, they're not going to have three months to hang out with the FDA. This is going to go from being the first time something like this has happened in world history, to something that happens 1,000 times a day.

Robert Green Every day.

END INTERVIEW ELEMENT OF PART TWO

So Ars Technica listeners - here we conclude the second installment of my interview with Robert Green - and of course, Part three is coming tomorrow.

As mentioned before, if you can't wait to hear the rest of the interview, you can just head on over to my site, at after-on.com. Or, type the words After On into your favorite podcast player, and scroll through the episodes to find this one, which originally ran on November 28th of last year. You'll also find lots of other stuff about life sciences - above all, genomics and synthetic biology. Conversations about robotics, privacy and government hacking, cryptocurrency, astrophysics, drones, and a whole lot more.

Or, you could just join me tomorrow, here on Ars.