

ROBERT GREEN INTERVIEW PART THREE - INTRO

Hello again, Ars Technica readers. This is the third and final installment of a three-part interview with medical geneticist Robert Green about 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 or two, there are links to them on the page where this player's embedded, and I strongly suggest that you go back and listen to those installments before this one.

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

Rob Reid Now there's also a wild and wonderful story about a condition that was discovered in a newborn that never would have been discovered otherwise, because this newborn was lucky enough to land in your program. Let's talk about that real quickly.

Robert Green: Sure, and this teaches us a couple lessons, including a real challenge to the notion of precision medicine itself. One of the newborn babies named Cora passed through newborn screening, the state program with the little heel stick, and was not flagged as abnormal on that, but when we did the exome on that baby, we found two copies of mutations in the biotinidase deficiency gene. That's a rare biochemical disease which means you don't process enough of a certain vitamin. You can get cognitive slowing, you can get intellectual deterioration, you can get awful skin disease, baldness, and even seizures, and even death. It can be a really terrible disease, and at an early age as a child. In its fulminant form, it can be terrible.

But when we tracked this down, we found out that the enzyme level in this baby was not low enough to have triggered the newborn screening flag, but it wasn't normal either. It was 40% of normal. Now here's the problem. We don't know if 40% of an enzyme level is enough for that child to live an entirely normal life. What do we do? I had no idea. Very little precedent.

What we ended up doing in this case was easy, because to treat this condition, all you do is give them a harmless vitamin, and that baby is now on this vitamin. But what we really don't know, because we don't have a trial in which we had 100 babies like this and we randomized half of them, we really don't know if we needed to do that. We are treating this in of one case in this situation. It's going to have a happy outcome, because it's a harmless treatment.

Rob Reid: You're going to do some enzyme replacement therapy.

Robert Green: We're giving the vitamin which boosts the-

Rob Reid: It's a simple vitamin?

Robert Green: Yeah. Simple vitamin.

Rob Reid: It's painless. It's riskless.

Robert Green: No harm, no foul.

Rob Reid: And you might have just saved this child a horrific and early death.

Robert Green: Well, probably the 40% enzyme level this child had was never going to declare the full disease. The question is did we save this child 10 or 15 IQ points?

Rob Reid: Ooh, which is valuable.

Robert Green: Which would have been invisible. This has got back to the question of fragments of disease, because we're used to identifying-

Rob Reid: It's binary usually we think of a disease. What it is with Huntington's, it's binary, but yeah.

Robert Green: It's like the piece of the iceberg that's above the water level. We're used to identifying that, but we're not used to looking for the unnoticed fragments of genetic disease. How many kids are out there with enzyme levels of 40% who would have been 15 IQ points smarter? We just don't know.

Rob Reid: Don't know yet. Well, and we may one day know if we get to the point where there's a standard of care all babies are sequenced, and we start wrestling with these issues. But again, we're not going to have your brain, the FDA, and all these other people in each one of them. There are going to be 150,000 of these edge cases.

Robert Green: We spent 100 hours on this case.

Rob Reid: On this one case.

Robert Green: One case with multiple experts, calling people around the world, but in fairness, that's what we in academia are supposed to do.

Rob Reid: Sure, you are.

Robert Green: In order to try to set some standards eventually that are agreed upon enough that all of the clinicians out there can get standards of care that are hopefully up to snuff.

Rob Reid: How many babies have you looked at now?

Robert Green: We've done a couple hundred so far now.

Rob Reid: A couple hundred?

Robert Green: Yep, and we're finding some scary variants. We're finding variants for heart disease. We're finding variants for cancer, and all these things are not present in the child, but they do add to the burden of risk that those families are going to have to live with with those children.

Rob Reid: Since we're talking about babies, let's do talk briefly about prenatal, this cystic fibrosis case that we talked about. When you think about cystic fibrosis, one person in 30-ish carries the gene, but you need two parents with it. It's recessive. That becomes a 1 in 900 chance to 1 in 30 chances. Then there's just a 1 in 4 chance that any given child that they have will get the disease. Now we're at 1 in 3,600, which sounds like a pretty low risk. But if you happen to be one of those carriers, and that's 3% of all living people, 1 in 30 people that you might take to the prom are also a carrier. If you're in that population, these numbers are very, very big. Knowing, having full wisdom about what one is carrying and what one's first date is carrying, maybe this becomes part of Tinder. I don't know, but certainly what one's spouse or partner is carrying, that becomes really game changing, doesn't it?

Robert Green: I think so. I think this is part of the low-hanging fruit of the genome revolution is that we should be aggressively pursuing preconception. We tend to use the word prenatal when we're talking about pregnant women.

Rob Reid: Preconception is-

Robert Green: We're talking about preconception screening.

Rob Reid: Much more important, yeah, because prenatal is, "Wow, that's a doozy." Now you're in all kinds of issues of-

Robert Green: Termination and-

Rob Reid: Abortion and on and on. So preconception-

Robert Green: Preconception screening. Now these ratios are different among different ancestry groups. Cystic fibrosis is not as high, for example, among African Americans and Hispanics, but the variants are different in ancestry groups that it attacks. It gets complicated pretty fast. It's all well and good to start spotting these preconception variations, except then we get back down into the mire of whether a particular mutation is actually bad or not. Remember, we talked about one single mutation for Huntington disease. We talked about four or so genes with multiple types of mutations for Lin syndrome.

The single cystic fibrosis gene has over 1,200 known mutations. That's just the ones we know about. You quickly get into some real complexity about saying this one's bad and this one's probably bad, and this one I'm actually not sure

whether it's bad or not. That's okay, as long as you're thoughtful about it. But if, again, when you try to roll this out in a scalable way, and when you're talking about some people possibly avoiding pregnancy or going and doing IVF, in vitro fertilization or maybe even terminating pregnancies on the basis of this, you're getting into some pretty serious territory. You start worrying about that ambiguity and that uncertainty.

Rob Reid: But there are a couple of amazing stories already with the relatively little genomic information the world has had. Can we talk briefly about Tay Sachs disease and how the Jewish community has almost eradicated it?

Robert Green: That's right Tay Sachs is another one of these recessive conditions where the mother has to carry a mutation, the father has to carry a mutation. It doesn't affect them at all.

Rob Reid: And overwhelmingly has tended to afflict people of Jewish descent.

Robert Green: That's right, Ashkenazi Jewish background. If they are each carrying it, each child has a 1 in 4 chance of having the condition. The condition is a horrible disease. It's a deteriorating neurologic disease that by age 4, 5, 6, kills the child in front of your eyes in an agonizing, neurological death. It turns out that by a combination of encouraging couples who don't carry the condition to reproduce together, by testing couples who do carry the recessive trait, by doing some careful in vitro, by this whole panoply of techniques, the Jewish community has actually managed to reduce the number of births of children with Tay Sachs dramatically.

Rob Reid: Like by-

Robert Green: I don't know the exact numbers.

Rob Reid: ... north of 50% or something.

Robert Green: I think so, yeah.

Rob Reid: A big, big number.

Robert Green: Yeah, a big number. Quite a bit. What this tells us is what George Church and others have been saying for a long time is that this is a tractable problem. We don't have to leave it to chance as to whether our infants are going to be stricken with a terrible recessive disease. The only gene that's actually routinely screened for is cystic fibrosis, and there are several others that are being advocated for, but there's thousands of these.

Rob Reid: Yeah.

Robert Green: There are several companies that are out in front actually promoting this, but again, the medical establishment appropriately cautious, perhaps, is lagging behind in advising it and advocating for it.

Rob Reid: Again, we get into issues of social equity. You had pointed out that cystic fibrosis is basically a white disease. That's the thing that we screen for. The Jewish community took it into their own hands to tackle Tay Sachs disease. I understand that there are now, in other communities of faith, for instance, there are efforts in predominantly black churches to start doing what the rabbis did with Tay Sachs with sickle cell anemia, correct?

Robert Green: Mm-hmm (affirmative).

Rob Reid: People are taking it into their own hands, and that's wonderful, but something that's much more widespread and perhaps society-wide could prevent a lot more damage across all races, all socioeconomic groups. Now you mentioned George Church. While I've been in town for a couple of days, you've been very, very generous, not just inviting me to the conference yesterday, but to that wonderful speaker dinner the night before. I had the amazing fortune to end up at a table with none other than George Church, who is somebody that I had known about for quite some time. He said something really interesting. To contextualize what he said, I was hoping you could just describe for people who George Church is.

Robert Green: Sure. George is a geneticist at Harvard Medical School who is widely credited with so many of the seminal inventions and technological developments of really our time, in terms of sequencing technology, in terms of gene editing, in terms of the concept of personal genomics. He really started the personal genome project, a kind of compendium where people can donate their genomes to be useful. He was really out ahead alerting people to the fact that they don't have much security about their genome, and they should just get over it and contribute to research.

His ideas, and in many cases, his influence or a specific assistance has helped launch scores of companies in the biotechnology space. He's even working on techniques for reversing aging. He's [protian 01:19:21] an incredibly accomplished scientist of our time.

Rob Reid: Yeah, and it's incredibly rare. I don't think I've ever delved into a professional community wherein if you ask, "Well, who is the greatest practitioner?" I've never seen such unanimity. It's almost like hockey fans saying Wayne Gretzky when he was playing, or basketball fans saying Michael Jordan when he was playing. Almost every profession is multi-polar, but when I ask that question about genetics, there is only one name that comes up anyway over this dinner. The conversation amongst the handful of us around our table turned to prenatal care.

George said, "Okay, this is a back of the envelope math, but it's roughly correct." This is George talking, so you know it's pretty correct. He said, "Roughly 5% of children are born with genetic conditions that are somewhere between quite bad and absolutely horrific." He said if the lifetime cost of care for those people on average rounds to \$1 million, if we do way preconception planning, if people are armed with information way before they're even thinking about marriage with somebody, let alone prenatal situation, if we can prevent those tragic conditions from arising in a newborn, lifetime of care, we're averaging \$50,000 of savings per birth. 5% chance, if you're unlucky, a million dollars in cost to society, to the insurance system.

We can sequence the genomes of mom and dad for a tiny, tiny sliver of \$50,000. That sliver is going to shrink and shrink as genome sequencing essentially becomes free. "Why wouldn't we," George said, "just make this something we do? We could preclude all these diseases, save all this suffering, all this healthcare?" What do you think of that calculus and that argument, I guess, in favor of ubiquitous whole genome sequencing?

Robert Green:

Well, I 100% agree with that vision, but of course George is able to work in the realm of pure science and hasn't had to wrestle with the medical system or the insurance reimbursement system, or all the practicalities associated with implementing this stuff in our society at large. Therein lies the rub. We don't have a medical system that incentivizes long-term savings like that. We have healthcare insurers who, on average, look two years out into the future before their client base churns to the point where they're not part of their plans anymore. It's a question of whose money would be saved? Therefore, who is incentivized to make that a reality?

Then there's the entire social construct that we've been discussing in the world of genomics. Is information toxic? Is it going to be misused? Is it going to be harmful? These questions keep recurring, often very appropriately, sometimes inappropriately, in ways that obstruct the implementation of these visions of the future. I think that's why he focuses so hard on preconception. Otherwise the management is either you shape courtship so that you don't even meet the people who are genetically at risk, which isn't very socially acceptable, or you do IVFPGD, which is 8, \$10,000 per system. People really don't necessarily want to conceive their children that way.

Rob Reid:

Yeah. It would be repulsive to screen out people who were genetically unattractive from dating, but it is not that people are sweepingly unattractive. It's just that a certain relatively low minority of people, given your personal genes, would happen to be a lousy choice for you. It's not like saying these 10% of people are genetically untouchable and these 90% of blessed people should all date each other. It's more that every single one of us has certain conditions that maybe precludes a small percentage. That's all very hypothetical.

You said something that I think is really, really important and kind of chilling. You mentioned the situation of people churning out of their insurance. You, I

believe, told me that the average American leaves their insurance plan on an average, what, every 24 or 30 months or something?

Robert Green: That's right. In some senses, even less. Even 15 months.

Rob Reid: Even 18 months. You end up in the dark, smokey back rooms of the insurance company that we don't get into. A calculus could be run that says, "Wow, for this relatively inexpensive test, we could potentially save a million dollars in lifetime costs. We might even save our customer's life." But guess what, this inexpensive test still costs money. We would be the ones paying for it, and we're going to be saving some other insurance company the money, because our patient's going to be long gone-

Robert Green: Long gone.

Rob Reid: ... by the time those savings are incurred. To hell with this. I think that's probably part of the reason why preventive care is much less of a priority for insurance companies than we would imagine, because they're making an economically rational argument, I mean arguably a morally repugnant one, but they're making an economically rational argument. If this preconception wisdom, which could, in some cases, avoid terrible outcomes, it's almost like it has to be like airbags. It almost has to be a society-wide or government mandate that says, "You know what? There are these inefficiencies. Insurance companies are going to do rational things." The value of this information is almost like herd immunity. The government mandates certain vaccinations, because they're only really good if everybody gets them. This might be something more like a vaccination.

Robert Green: Oh, that's right. Remember, there are obstetric societies who are actively grappling with how far to extend the recommendations for it, but we also don't really need to ascribe nefarious motives to the insurers, because they also need to draw the line somewhere, because the narratives of things that may prevent illness far exceed the evidence of things that prevent illness. They can't really reimburse for narratives. They have to reimburse for things in which there's evidence. That's a tougher problem in genomics than in some other areas. You have short-term interventions for short-term outcomes. You want to test a new antibiotic? You get 1,000 people with an infection, you test the antibiotic, you see if within a week or two their infection clears up. Bading, badang. You've got the question asked and answered. We're talking about stuff that amortizes over decades.

Rob Reid: Now I want to close just discussing a couple of really non medical risks that are associated with this information. Equifax, which Americans trusted with vast amounts of the most intimate financial data that most of us have, rather moronically allowed it to be shared with criminals. This was a company that was allegedly in the safety business and the data safety business. When you're sitting on top of the social security numbers, credit ratings, and radically detailed intimate financial facts of hundreds of millions of people worldwide,

you would imagine a company like that wouldn't make its passwords "administrator", which I believe was the case in one case.

We've seen companies that are allegedly unbelievably sophisticated about data security. Now we're talking about a world in which one day most of us will have this really important data, which is our genome. Maybe Equifax is going to be looking after that thing. It's probably going to be stored in the cloud. It might be stores in many clouds. If my baby's genome is sequenced, by the time my kid is a junior in college, it might be at his old pediatrician, at the nurse's office of every school he or she has gone to. It could be all over the place.

Robert Green: Could be at the gym, at the grocery store. It could be anywhere.

Rob Reid: What do we do about data security in situations like that? What do we do about discrimination?

Robert Green: The first thing is to not expect perfection. I think that just as health information has been hacked, the former governor of Massachusetts had his hospital records hacked. The genomic information is going to be vulnerable. What's interesting in this discussion is the psychological burden of discrimination fear in genomics. In this BabySeq project, we were talking about we did this heroic effort where we walked into almost every one of 8,000 babies born a year at Brigham and Women's Hospital. The percentage of families that said yes was 6%.

Rob Reid: You cast a wide net. You said, "Would you or would you not like to have this information?" And 94% of people said, "No, thank you."

Robert Green: Yeah, and it was a little more complicated than that, because a lot of people this is a stressful time in their life. They've just had a baby. This is the Dellinger principle. We went where the babies were. A lot of them said, "No, get out of the room. I don't want to talk to you. I'm breastfeeding no." Another group of them said, "I don't want to participate in any research. I'm tired." And a lot of people said, "Oh, you mean I have to come back? No, I don't want to come back." A lot of reasons. But among the non-logistical reasons, the number one reason was fear of future privacy invasions and insurance discrimination.

These fears are inhibiting people not only from getting tested, but from even participating in the critical research to get tested. We're going to have an experiment at scale of this very soon, because the precision medicine initiative now renamed all of us Research Program.

Rob Reid: Folks won't know what that is, or some will, but some will not. Could you give a quick overview of what it is?

Robert Green: This is a one million person cohort that is being sponsored by the United States government and NIH and the 21st Century Cures Act to try to enroll a million Americans in a longitudinal study and study them from every direction. Study

their genomics, study them with FitBit, study their electronic health records, study them with blood tests, and really give back to those who want it any piece of this information. That means giving back genetic information, if they want it.

Rob Reid: A million people will go through this.

Robert Green: A million people.

Rob Reid: How long is that recruiting expected to take? There's only a few thousand have been recruited in already, right?

Robert Green: That's right. The formal launch of the study isn't until the springtime, but it's going to go for years.

Rob Reid: But it'll take years to get the million people in.

Robert Green: Years to get the million people in. Hopefully years of following them all up and keeping them in, and years and years of exciting data for scientists all over the world to analyze.

Rob Reid: How are they picking these million people, or is it really just whoever comes in the door, because we want such an immense diversity? Although, you will not get an immense diversity if you just take those who are coming through the door.

Robert Green: That's exactly right.

Rob Reid: Because they're going to self-select. How are they selecting them and recruiting them?

Robert Green: Program is very focused on representing populations that have historically not participated in research. That's just an incredibly noble aspirational goal. Underrepresented minorities, homeless people, poor people, handicapped people, people who don't particularly participate in research will be sought out and encouraged to participate.

Rob Reid: If anybody listening to this is an information seeker and likes the idea of being a subject in this enormous project that will, if done correctly, benefit many generations of humans, is it possible for people to volunteer for this program? Would you expect that it will be, when it gets launched in the springtime?

Robert Green: Absolutely is, and in fact, it's in its alpha stage right now. Anybody who wants will be able to volunteer. Then a certain enriched component will be carried on into the next stages. People can go and Google All of Us Research Program. They can see exactly how to do that, even now.

Rob Reid: Wow. Interesting. This has been a fantastic and fascinating discussion. As much as I have studied up on this stuff in preparation for this conversation, I've learned a ton in the last hour and a half. Thank you very, very kindly for your wild generosity with your time, not just today, but in getting me up to speed and inviting me to your wonderful conference yesterday, and inviting me to the wonderful dinner the night before. I wish I could do this much research for each and every one of my interviews. I'm certainly delighted that I was able to do it in this case, and you enabled all that with your generosity.

Robert Green: Well, you've been an inspired and inspiring student for all of this. I learned an equal amount from your wonderful novel and have had a great deal of pleasure in meeting you and chatting with you about all of this.

Rob Reid: Thank you very much, Robert.

So much information in that conversation, but so many questions raised as well. I guess the biggest one, for anyone who can comfortably spare \$1,000 is should you get your genome sequenced tomorrow? You might learn something completely deterministic about yourself with high or even total penetrance. A Huntington's diagnosis, for instance, or you could be warned of an incoming bullet and then dodge it painlessly and effortlessly, like that baby who may have picked up 15 IQ points as a result of landing in Robert's study. Should you do it?

Today, that question has no definitively right answer. I think Robert made that point very powerfully. It depends very much on your own psychology, your hunger for information, and your tolerance for uncertainty. It also depends on your financial situation, as this is almost certainly not something to do if \$1,000 would significantly strain your budget. But while there's no right answer today, the cost benefit balance will swing relentlessly in favor of getting the information over the coming decade. The financial cost will continue to plummet, and the actionable data that we get, as opposed to just the despair inducing data, will grow steadily.

It'll be kind of like smart phones. It'll seem like a deluxe novelty for a while. Then you'll get it. Before you know it, folks who don't have it will start seeming a little weird. I don't know how well-prepared the professional genomics community is for this. Robert talked about the controversy about providing consumers with their own genetic data. It was pretty clear to me, from hanging around that conference, that with many people, this controversy has not yet gone away. I'll add that to most attendees, not all, but most, a world in which full genome reading is standard medical care seems like a distant hypothetical still. This is actually unsurprising. Most of these folks have worked in genetics for decades. During that time, the number of everyday people who have had their full genomes read has gone from zero to, at most, virtually none. Do you know anyone who's had their whole genome read? If you do, you probably live in one of four or five coastal cities and know a lot of one percenters.

When you see a phenomenon go from non-existent to incredibly rare over 30 to 40 years, it's natural to assume it will take a very long time, even centuries for it to become ubiquitous. For similar reasons, if you went to, let's say, a computer networking conference in, I don't know, 1990, and asked the corporate IT heads who went to those things back then how many Americans would be on the internet in 20 years, nobody would have said most of them. The internet had existed since the '60s, and its entire consumer population could probably fit in a bus in 1990. But then look at what happened.

In the case of genomics, it's true. The cost of sequencing an individual genome has dropped from \$3 billion to \$1,000 in less than 15 years. But from the standpoint of most everyday consumers, the difference between those prices is kind of academic, because at 1,000 bucks, there's still a 0% chance they're going to get it done. But that changes radically as you move from 1,000 bucks to basically free which is where we're heading over the coming decades, maybe even faster.

That's it for now, but if you're interested in your health or in your mortality, you'll want to listen to the next episode, in which we will talk about living forever. Yes, really. Until then, please try to stay healthy.

END INTERVIEW ELEMENT OF PART THREE

So Ars Technica listeners - here we conclude the third and final installment of my interview with Robert Green. I do hope you enjoyed it .

If you're curious about the latest episode in main After On podcast feed – this week it's an especially fascinating conversation, which I think will really resonate with Ars Technica readers. It's an interview with an ornithologist at Yale, whose deep engagement with biological history has given him a rather heretical take on Darwinism. Ironically, a take that Darwin himself would have almost certainly whole-heartedly endorsed.

If like me, you're fascinated by the field of evolutionary psychology, or the deep processes that shape the forms of behavior of life, I think you'll find it truly fascinating. To hear it, head on over to After-On.com, or search for After On in your favorite podcast software.

And/or - join me here again on Ars next week. When we'll be serializing that very episode.