ROBERT GREEN INTERVIEW PART ONE - INTRO

Hello Ars Technica listeners. This is the latest serialization of an episode of the After On podcast. We're splitting this one into three segments, starting today. And I'll be talking to medical geneticist Robert Green

Rob Reid:

Our interview covers issues which are very complex and aren't widely understood, but despite that, they're likely to become personally relevant to almost all of you over time, and that's a rather odd claim for me to make because this certainly is not a self-help podcast, but today's episode will give you context on a wildly complex avalanche of intensely personal, factual data that you can expect to receive about yourself in the coming years.

I'm talking about the contents of your genome. The cost of reading our genomes is falling so quickly, and the actionable insights that come from this are growing so fast, that within a decade or so, obtaining this data will be as mundane and common as checking your cholesterol levels. This will let you and your doctor know the precise contents of your 20,000-ish genes. Since some human genes literally have thousands of known mutations, this is a lot of data, and we won't know what to do with most of it on the day you receive it. In fact, we'll be lucky to glean even 1% of the life and death facts that genomes will eventually reveal to people, say 40 to 50 years in the future.

But we will start gathering this data en masse because in most cases, it will be better to know something than nothing, but not in all cases because your genes could very reliably foretell a horrible fate for you, a fate that you can do absolutely nothing to avoid, perhaps in your near future. But the opposite could also happen. You could learn of a horrific condition that you can easily avoid with a painless and effortless intervention if you start taking steps today.

These aren't hypothetical quandaries. You could yourself in either of those extreme situations this week if you drop 1,000 bucks and become one of the relatively fewish pioneers who are choosing to have their genomes read in a relatively primitive time. Robert and I will discuss present-day cases representing both of these outlier situations in our interview. We'll also discuss how the crushing majority of data that the crushing majority of us can get from our genomes is currently ambiguous, and depending on how you're put together, this ambiguity could be psychologically awkward. Awkward enough that some very expert and caring people have treated genetic information as a toxin. That's right, medically toxic information. Though that sounds like a euphemism, the field of medical genetics conducted itself as if toxic information was a literal phenomenon for many years, and many people in that field still do.

My guest today, Robert Green, has given all these issues more thought than almost anyone. He has many affiliations. He directs the Genomes to People

research program. He's a medical geneticist at Brigham and Women's Hospital in Boston. He's a professor at Harvard Medical School, and an associated member of the Broad Institute. Broad is a fascinating entity, which Robert will describe at the start of our interview.

Now, more than just sitting down for this interview, Robert graciously invited me to attend a day-long genomics conference, which he hosted at Broad, which we'll refer to a couple times in the interview. He furthermore invited me to the speakers' dinner the night before that conference where there were lots of talks and information exchanged and so forth, plus he was boundlessly available to me in person, over the phone and via email as I prepared for this interview.

I wasn't coming into this as a novice. I've read dozens of books about genetics over the years and even took an online genomics course from MIT, taught by none other than Eric Lander, who founded the Broad Institute. Despite all that background, I learned a ton in the course of all this, and I believe the core of what I learned is almost entirely conveyed in the interview you will now hear. So I believe that, like me, you will now find Robert Green to be an exceptional teacher.

Just a couple more words of context before the interview starts: As you may know from previous episodes here on Ars, my podcast dives deep into complex issues in science, tech and society which are worth understanding a bit better. Each episode's built around an in-depth interview with a world-class expert in the relevant field**.** I do 20-30 hours of up-front research and preparation before sitting down with my guests. And I structure my interviews carefully, so that their information density hopefully feels a bit more like TED talk than a meandering long-form interview.

And with that, let's start my interview with Robert Green.

Robert, it's great to visit you in your office for the second time here. I'd love it if you could start out by telling us briefly about this remarkable place that we find ourselves in called the Broad Institute.

Robert Green: Well, the Broad Institute is the Broad Institute of MIT and Harvard, and it's the brainchild of Eric Lander, a famous scientist in genomics and mathematics. It's really a place where he's envisioned investigators from all sorts of disciplines in the Boston Area coming together in a free exchange of ideas in ways that perhaps their home institutions don't readily encourage quite as easily. So it is an addendum to their home institutions, a supplement, a kind of add-on, a synergistic place rather than a competitor. I think that vision has largely come true. It's a fantastic place where those of us who have primary appointments, as I do at Brigham and Women's Hospital, can have also an affiliation with the Broad Institute, and really improve our work, grow our work, augment our work there.

Rob Reid: And the institutional affiliations get a little complex. So yours include being director at the Genomes to People research program, a medical geneticist at Brigham and Women's Hospital, a professor at Harvard Medical School, plus you're an associate member of the Broad Institute. And it's worth noting that Brigham and Women's Hospital is not strictly a women's hospital.

Robert Green: No, not at all. Brigham and Women's was historically two hospitals: Peter Van Brigham and the Women's Lying-in Hospital, which combined together some decades ago, and now has the awkward name Brigham and Women's Hospital, but its one of the two major teaching hospitals in the Harvard Medical School system, the other being Massachusetts General Hospital.

Rob Reid: Well Broad is primarily about genomics. Is that fair to say?

Robert Green: Yes, it is.

Rob Reid: It largely is. Yesterday in a presentation, a colleague of yours shared an astounding statistic. She said on average, the Broad Institute reads an entire human genome every 10 minutes, which is quite a feat but a common feat these days. It always blows my mind because the first time, it took the entire life sciences community 13 years and $3 billion to do that, and that wasn't in the 1930s. That was in 2003. So obviously, we've sped things up a little bit, but even more amazing to me, as a Silicon Valley person, she said that you guys have now 45 petabytes of data.

Compare that to YouTube, which has 86. So you're over half the data foot print of YouTube. That's meaningful to me because in tech, we talk about YouTube's storage capacity kind of the way I imagine governors talk about Alaska's land mass. It's just this thing that's so big, it's senseless to compare it. And you're already overtaking them. That is so much storage. And your own research, I think about it as being confronting and figuring out what to do about the terrifying ambiguity that substantially all humans are going to face on the inevitable day, whether it's 10 or 15 years from now, when we get our genomes read and we face all this data.

What do we do about that ambiguity? How do we reduce it? How do we deal with it? Is that a fair enough summary of the thrust or your research here?

Robert Green: That's exactly right. The Broad and other genomes centers are cranking out data on thousands and hundreds of thousands of people at an incredible rate, but my mission is when you take that individual genome, and you try to apply it to the health of a human being, there is a different kind of huge data for that one genome and that one person. There are three billion letters, and even though they're 98 or 99% the same for all human beings, that means there's three or four or five million places where they vary between human beings, and that is an awful lot of complexity.

The question is how do we take that complexity and apply it in a sensible way to the health of human beings?

Rob Reid: What's chilling about it for many people is as they approach this information, is the possibility of bad news when they find out what their genes quote unquote say. That bad news isn't about the stock market being down 5% or their car needing repair. It's about disease and death that might hang over their heads or that of their children or their descendants or something like that. So this is non-trivial information, and it is wildly complex, and the conveyance of that information has to be done with incredible sensitivity and care. The problem is, we don't know what such an enormous percentage of it means yet.

Robert Green: That's right. And the beginning of genetics, the beginning of medical genetics at least, was all about the deterministic mutations, those changes in the DNA that meant you would definitely get a particular disease. We talked a little bit about Huntington's disease, which is a fatal, horrible neuro-degenerative disease that robs you of your sanity and your behavior and happens in your 40s, 50s, 60s. It's pretty awful.

Rob Reid: And if you've got a certain configuration of the Huntington gene, quote unquote, you are going to get it. End of story. And we can't do anything about it.

Robert Green: That's exactly right. It's actually a done deal. You might have a little variation on the age of onset, but if you've got the mutation, you will get the disease.

Rob Reid: Who would want to know they have that. If I were 25 years old and that sort of Damocles were hanging over my head in the 20-year future, personally, and I think this would be true of a very high percentage of people, I'd sure like to not know about that, and that's the kind of things that people can discover. Now, you used the term deterministic. This type of disease in which it is locked and loaded, no way out, when it comes down to solitary gene, simple case like this, it's called monogenic Mendelian, right?

Robert Green: That's right. So Mendel and his peas actually deduced these laws of dominant and recessive inheritance.

Rob Reid: Mendel being the father of modern genomics.

Robert Green: That's right.

Rob Reid: And it wasn't his peas that did it. It was with the help of his peas.

Robert Green: That's right. So a dominant condition means that when you have one copy of the mutation, remember you get two copies of every gene, one from each parent, but when you have one copy of a bad mutation, you will get the disease if it is 100% penetrant. And that's another term that everybody's eventually going to have to learn about, which is if you have the mutation, do you get the

disease? In the Huntington's disease example, it's 100% penetrance, meaning you definitely get it.

Rob Reid: And it's a fairly extreme example in that 100% penetrance, correct?

Robert Green: That's right, and you asked, "Who would want to know?" It turns out that when the first gene testing for Huntington's disease came out, they had asked all the Huntington relatives-

Rob Reid: People who had it in the family.

Robert Green: Uh-huh, had it in the family-

Rob Reid: And knew they might get it.

Robert Green: Knew they were at risk. They said, "Hey, there's a test coming. Would you want to get it when the test comes?" And lots and lots of people said, "Yeah. I want to know." It turns out that by an order of magnitude, people did not show up and did not volunteer when that test became available.

Rob Reid: Interesting. They said hypothetically they'd like to know, but ultimately, they elected not to.

Robert Green: That's right. And so the whole Huntington's disease example is incredibly important to understand how modern genetics has evolved because number one, it implanted in everyone's mind the notion that genetics was destiny. If you had the gene change, you were going to get the disease.

Rob Reid: And also this nomenclature that people outside of the field, like myself, use. The gene for this. There is a Huntington gene. There is a curly hair gene. There's a smart gene. But it's not like that. Huntington's is a very clean example.

Robert Green: It's a very unique monogenic example, and it was unique for another reason. It was terrifying. So when you sat down with a family, like imagine yourself as a geneticist or a genetic counselor sitting down with a family to give them the news. So it's, "Mr. Reid. I'm sorry to tell you that you are carrying the gene for a mutation for Huntington's disease." Think about that moment. People would dissolve into tears. People would go off and become depressed. There was a fear of suicide. This was probably the most terrifying information you could get. It colored the experience for both the entire field of genetics as well as of course all families who had to get this information.

Rob Reid: Because this was one of the earliest tests, and the other earliest tests were also these relatively simple, clean-cut examples of a gene does this with 100% penetrance. Now we're going back, what 70s, 80s when these tests first came out. But that was all there was for so many years, it did shape people's minds. I

would imagine the doctor or the counselor delivering that news, that person would get PTSD from this.

Robert Green: I've almost thought the same thing. That there is a kind of a crude trauma for the provider in confronting the trauma of the family member. This helps us understand why genetics and genetic counseling arose as being so careful about information, so respectful of the way that information was given. Now, in the meantime, this wasn't happening in all the rest of medicine. I mean, we try to be sensitive when we tell somebody, "You have cancer." We try to be sensitive when we tell them, "You have Alzheimer's disease," or AlS or any of a number of horrible diseases, but we just don't tiptoe around the information in the same way that genetics has learned to do that.

It's partly that trauma of early Huntington's disease families, but I think there's another element as well, which is that it's about reproduction in many situations. The other side of monogenetic conditions is that people are carrying recessive carrier traits, meaning I'm carrying, perhaps, a cystic fibrosis mutation. It's not going to do anything to me, but if I have a child with someone who's also carrying a cystic fibrosis mutation, then we have a one in four chance of having a child with cystic fibrosis, and this is both frightening and predictable.

So this genetic counseling rose up to talk to people about the probabilities that you would get these recessive conditions, and to sensitively talk about reproductive options because suddenly, you're dealing with people who are in the timeframe of pregnancy who might want to consider termination, who might want to consider surrogacy. Who might want to consider a whole bunch of sensitive topics.

Rob Reid: Or adoption. I'm adopted myself. These are massive familial decisions.

Robert Green: Very emotionally laden, and you want to get it right. So genetics has grown up technologically, but it's also had this incredibly vibrant emotional sensitivity to the potential toxicity of information, which is I think a fascinating arena to be discussing this.

Rob Reid: What's interesting is Huntington's disease, thank God, is very rare. Most people probably haven't heard of it. Those who have, like me, have almost certainly, the majority of them, heard about it in the course of learning a bit about genetics. So that's rare, thank God. Cystic fibrosis, the carrier rate of recessive gene is one in 31, somebody said yesterday?

Robert Green: Yeah, one in 31, one in 33. Somewhere around there. It's very common.

Rob Reid: That is a lot of people. Now, when you say one of those people has to meet another one of those people, so now we're one in 900, and then there's a one in four chance, the odds start diluting, but most people, let's imagine in the 10 to 15-year future, when getting one's genome read is a standard operating

procedure like cholesterol, a lot of people are going to find out long before they're thinking about reproductive health, maybe when they're 16 or 17 or 18. They're carrying this monster. It won't affect them, but boy, is that going to be in the back of their minds probably forever. Certainly when they start dating somebody seriously. There's a one in 31 chance that this person's got it. It really transforms stuff.

Just before we wallow too much in dismay, I'd like to pivot to the inverse of the Huntington situation to sort of like a hero case. Again, a simple condition, a monogenic condition with high penetrance, which could save your life by learning about it early because there's that side as well. You were telling me about something called Lynch syndrome.

Robert Green: That's right. In this case, there are four or more genes, not just one like in Huntington's disease. And these are DNA repair genes, which if broken by a mutation, tend for some reasons that we don't fully understand, to give you increased risk of cancers. Now, the cancers aren't totally restricted to one organ, but the most common cancer that you get with these is colon cancer, and that's bad news because it puts you at a highly increased risk for colon cancer, but it's good news because with regular colonoscopy, that scope that that goes up and looks in your colon for early tumors, you can actually nip these in the bud, catch them, excise them and save people's lives.

Rob Reid: Yeah, and the risk goes up to an astronomical rate. Isn't that people with certain mutations have literally a 60 or 70% chance of developing colon cancer, right?

Robert Green: That's right, depending on how long they live, whether they already have it in their family, and other things like that, there is a very high risk of developing colon cancer.

Rob Reid: And then while I'm sure most people don't think of a colonoscopy as a fun way to spend an afternoon, there is anesthesia, I'm sure. That is something that is like you're just careful about it. It's like brushing your teeth. You maintain yourself. And if that person had gone to a genetic counselor early in their life, they'd literally in many cases will have had their lives saved.

Robert Green: Absolutely, and the lives of potentially their family members.

Rob Reid: Right.

Robert Green: One of the great things about genetics, I actually argue that genetics should be more like the rest of the practice of medicine, that we should de-exceptionalize genetics as much as possible, but one of the undeniable areas where genetics is different is that if we identify a mutation in someone who has 12 brothers and sisters, we know that on average, half of those brothers and sisters are going to be carrying it as well. So you really can not just save the life of the one person

who's gotten tested, but you can propagate that information by testing siblings or cousins, adult children, whatever, in order to hopefully save their lives too.

Rob Reid: What a noble thing to do. Now let's move into something I'm going to call scary but useful. That's a medical term that I invented myself by the way. So a condition that presents hard choices, maybe agonizing choices, if caught early, but can in many cases save lives. Now we're getting into the realm of ambiguity, which is really where 99.something high percentages of this information dwells in this realm of ambiguity. BRCA is an example that a lot of folks are familiar with because celebrities have been dealing with it and so forth. Certain mutations of this gene correlate very highly with breast and ovarian cancer. Would you care to talk about that situation?

Robert Green: Sure. It's always emotionally loaded because there is a treatment, or preventative actually, and that preventative is surgery, to have your ovaries or your breasts removed is of course a major surgery and emotionally difficult event to say the least.

Rob Reid: Yeah, it's bilateral mastectomy. Your ovaries are removed. It brings on immediate menopause, right?

Robert Green: Yes.

Rob Reid: This is an issue that sometimes very young women are facing. That will eliminate the risk of cancer developing. What would the ongoing risk, if somebody said, "I'm going to do that Lynch syndrome thing and just monitor closely. What is the risk that they incur if they do not have these fairly radical and certainly traumatic and incredibly intimate surgeries?

Robert Green: Well, a lot of women do opt with their oncologists for close surveillance. So they will get scans on a regular interval, much more regular than is advised for unaffected individuals. Many people feel that they will be able to catch cancers early and contain them, particularly the breast cancers because remember ovarian cancer is very hard to spot early. I think the jury's still out on exactly how effective it is to maintain that kind of surveillance. Sometimes when you catch the cancer, with even the best surveillance, it has already spread.

Rob Reid: These are incredibly high numbers. If somebody doesn't know that they carry this gene, again they have something crazy like a 70% chance of eventually developing one of these cancers.

Robert Green: That's right, so that's kind of the worst-case scenario. These are generally people of Ashkenazi/Jewish descent. They are carrying a BRCA mutation at a pretty high rate. Between one in 40 and one in 50 individuals are carrying it, and if they have a family history of breast cancer, then the penetrance, the probability that they will develop cancer, can be as high as 70%. What is a little more in debate is if they don't have a family history, and you find a BRCA 1

mutation for example, is the penetrance going to be as high? Most people think it's lower, but still high, like maybe it's 50 to 60&.

When you are facing issues like mastectomy, you really would like to know what your odds are. You really would like to know the facts. Even knowing the facts, it's a horrible decision, but it's even worse if a clinician tries to tell you in all honesty, "You know what, I don't exactly know how common this is likely to be in your given situation."

Rob Reid: And we are, at this point, just barely tiptoeing into the land of ambiguity from the clear-cut cases, the highly penetrant ones. One other one I'd just like to hit real quickly because it's similar to BRCA and it was an example that I was not aware of until you told me about it, are long QT syndromes. Another interesting case in which you face a hard decision because the curative step is not without risk and complication.

Robert Green: That's right. So these are syndromes where you can actually, your heart can stop and you can have sudden cardiac death.

Rob Reid: At an early age, right?

Robert Green: Even as young as childhood or adolescence, absolutely. So that's a terrifying thing, and it can be brought on by exercise, for example. So you read those cases of a high school basketball player who has collapsed on the court and died. Those are generally this kind of condition. So you say, "Well, wouldn't you want to know about that?" Well, of course you'd want to know about that, but let's dig down a little bit.

It turns out there are a dozen or so genes that can cause this, and there are literally thousands of different variations, different kinds of mutations that each of these genes can have, and suddenly you realize that you are dealing with a lot of ambiguity in any given individual. So this given individual has what looks like a bad mutation in a long QT gene, but they don't have any family history. Nobody ever died suddenly. What do you do about that? Right now, there's simply no precedent.

You could go to three cardiologists, and one might say, "Don't worry about this. You don't have a family history, and this variation hasn't been seen very often. Just go about your normal life." A second cardiologist might say, "Hm. That's concerning. Let's get an EKG every year, and maybe you should rethink that professional basketball career." A third cardiologist might say, "Boy that's really scary. Out of an abundance of caution, we're going to implant a defibrillator into your chest with wires in your heart so that if it ever stops, it will automatically shock you back into a normal rhythm. Those are three completely different approaches to the same patient, and medicine doesn't do well with that kind of uncertainty.

Rob Reid: And the third one, which in many ways is the most cautious one, it might be sort of the comparable to the bilateral mastectomy and ovary removal in BRCA, is not without complications. It's not without risks because I imagine sudden cardiac death syndrome is just as bad as it sounds.

Robert Green: Yeah. It's death.

Rob Reid: A lot of diseases have these ambiguous names, but there's very little ambiguous about sudden cardiac death syndrome. So is that considered to be the conservative approach to get that defibrillator put in when this is a significant possibility?

Robert Green: Well, it isn't yet, but this is part of the question of the coming genomic tide of information, and it all depends on what you think the probability is that that patient in front of you is going to development that cardiac destiny. So look, if you think its 50%, put that sucker in. But if you think it's 5%, and we'd have to put in 20 of them in order to save one life, then you start questioning. If you think it's a tenth of one percent and you've got to put 1,000 of them in to save one life ... Might we lose somebody on the operating room table? And if it gets much smaller than that, you're probably doing more harm than good because by virtue of anesthesia reactions and putting people under major surgery and these things going off on their own when they're not supposed to and stopping your heart, you could actually kill more people trying to protect them than you would actually protect.

Rob Reid: And a critical semantic change here. You have pivoted from using the word "know" to using the word "think" because we've left this deterministic realm. I wanted to just reiterate the point that you made. Three ingeniously, wonderfully trained cardiologist looking at the same data, could easily come to three radically different conclusions because we've left the world of know and entered the world of think. I'm just going to cite that awesome statistic one more time. Back when it cost $3 billion and took 13 years to sequence an entire genome, people didn't get that done, so they stayed with those teeny tiny, very narrow, highly surgical tests, which were affordable back then, like the gene for this 100% penetrant disease called Huntington's, and now we're getting into the realm of the $1,000 genome.

Robert Green: Right.

Rob Reid: Where again, we've just tiptoed into the realm of ambiguity. Now let's go into it whole hog. The polygenic disease, or as I heard people call it at the conference yesterday, common disease. Is common disease actually a technical term that means a non-monogenic disease?

Robert Green: That's right, so people call it common-complex conditions or common-complex diseases. By that they mean that there are complex ideologies. It's usually a combination of many genes and some environmental factors.

Rob Reid: Tell us what many means.

Robert Green: It can mean hundreds, and the larger your data sets are in these studies that ascertain these small-effect size genes, these genome-wide association studies, GWAS or geewas studies, the larger your populations get in these studies, the more genes you can discover. So for example, ordinary coronary artery disease. The thing that gives us all heart attacks as men. It's probably going to statistically going to kill you and me. There are well over 100 genes that have been identified, but unlike the monogenic diseases, unlike the one's we've been talking about, each one increases or decreases you risk just a little bit.

Rob Reid: By a sliver of 1%. Yeah.

Robert Green: You can imagine a bell curve in your mind. At the middle of the bell curve, you have 50 slight risk genes, and 50 slight toggled the other way, and they're protective. So you're kind of neutralized. But you can imagine by chance, people over in the tails of the bell curve who have a lot of protection because they're just lucky and they've got all of the switches flipped to the protective side, or on the other tail who are just unlucky, and they have all their switches flipped to the risk side. And when you get way down in that tail, you actually start to approach the risk of some of the monogenic diseases. So you get a 3X or 4X risk, but only in that tail.

Rob Reid: Only in the extreme cases. Compared to this, hundreds of genes interacting, and by the way let's not forget it's roughly halfish of disease risk kind of comes from genes, and correct me if this is wrong, and roughly halfish comes from one's environment and one's behavior and how one has lived one's life.

Robert Green: Yeah. I don't know how to quantify it, but that's a good way to think of it, that there is a substantial genetic component to even the common diseases like heart disease and diabetes, and there's also a substantial environmental component.

Rob Reid: Yeah, and so when we were looking at that wildly straightforward example of long QT syndrome where there's a teeny handful of genes that genomically informed cardiologists probably look at a lot and they can have wild disagreement, when we get into the realm of the common diseases, which are common, which are the ones that almost all of us are going to be afflicted with, there is absolutely no certitude, even if you had access to the 10 greatest geneticists in the world.

Robert Green: That's right. They're a combination of multiple variables, but the essence of both of these domains is that we are talking about probabilities, and in many cases, we don't even know what those probabilities are.

Rob Reid: How many people at this moment would you estimate have had their entire genome sequenced?

Robert Green: You know, you have to think about whether it's research or clinical, but probably in the order of one and a half to three million genomes/exomes have been done in the world, and then in terms of patients where you're actually doing it for medical reasons, I don't know, I'm guessing a couple of hundred thousand.

Rob Reid: Right. And so on top of that, in order to start getting the kind of data that we would need to get rigorously statistical information, you would not only need a very large number of genomes sequences, but just as vitally, you would need to match them to incredibly meticulous health records of the sort that probably fewer than 1% of us even have. So to start saying, "Okay. We've looked at this vast sea of genetic information. We know this factually. A one-eighth of one percent chance increase that you're going to have a heart attack," you need to know a lot of genomes and a lot of radically detailed health records, and we're nowhere near that at this point.

Robert Green: That's right. It's important to keep in mind that we're not just talking about the 20,000 or so genes in the human genome. We're not just talking about five to 8,000 genes that have been associated with diseases. We're talking about sometimes hundreds or sometimes thousands of individual mutations or variations in each one of those. If you multiply all of those things out, you really realize that no population is going to be big enough.

We can definitely improve our resolution of gene disease association, gene phenotype association by getting larger numbers, and we need to do that. But we're also going to have to develop more basic science ways of understanding why is it that a particular mutation causes disease for one person at 40, causes disease for another person at 70, and for a third person, the exact same mutation doesn't cause disease at all.

Rob Reid: Because there could be 99 other genes in play, right.

Robert Green: That's right. There's other genes in play. There's environmental triggers. So unfortunately, the genome, which we had huge hopes for in terms of predicting and preventing disease, let's be clear, it's going to help with some, but it's the beginning of the story. And it's the skeleton, if you will, it's the template, the static blueprint on which the entire orchestra of functional biology is built and is interwoven through the proteins that are being made as a result of the blueprint, through the interactions of those proteins, through the metabolic interplay between the networks of those proteins, and on and on, with levels of complexity that we are only grasping the extent of.

Rob Reid: And just to drill down on one thing you mentioned in case some folks don't have a full picture of how this would happen, you would make the case, some folks don't have a full picture of how this would happen. You had mentioned that certain genes could have thousands of mutations. I think sometimes people hear that and they're like, "Wait, isn't the gene like a thing, and it's mutated or it

isn't"? The fact is that each gene has several hundred at the absolute minimum, but usually several thousand letters in it.

Robert Green: Right.

Rob Reid: And any one of those letters could be a mutation. So, when you have a chain that's comprised of, let's say, two thousand links, and some percentage of them could be damaged in different ways, that's where the amazing complexity comes into, and that's why any one of these twenty-something thousand genes could literally have thousands of different weird things that are atypical of it. So now again, we're way outside of this deterministic 100% penetrance world, and this is the world we're going to inhabit forever.

Robert Green: That's right.

Rob Reid: Because we are never gonna get to a point of perfect certitude, not in our lifetimes anyway, about how all these things interact.

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"?

END INTERVIEW ELEMENT OF PART ONE

Hello Ars Technica listeners. Robert and I will continue our conversation tomorrow. If you can't wait to hear the rest of it – or, if you'd like to browse my other 30-ish episodes, you can just head on over to my site, at after-on.com. Or, type the words After On into your favorite podcast player. This interview 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.

If you like what I do, I hope you'll consider subscribing to my podcast and listening to some of the episodes in archive - all of which were designed to have long shelf lives, and none of which have gone stale yet.

And of course you can join me here tomorrow on Ars, when we'll continue with Part Two of this interview.

END MUSIC