Personal Genome Service Providers
Dietrich Stephan, Ph.D.

MS. AU: We are going to continue the session on personal genome services. The next session is a roundtable with the five companies. Each of the companies will present for approximately 10 minutes, less if you can do it, and then we will have a question-and-answer period after everyone has presented.

Just like the NFL, we are going to give them a two-minute warning before the end of their talk, with no timeouts. A two-minute warning with no timeouts.

Our first speaker is from Navigenics, Dietrich Stephan. He is the co-founder and chief science officer at Navigenics. Prior to his current role, he was the deputy director of discovery research at the Translational Genomics Research Institute and still holds a faculty appointment there.

Through his research Dr. Stephan has identified genes and contributed to the understanding of genetic predisposition for multiple diseases.

Thank you for being here, Dr. Stephan.

DR. STEPHAN: Thank you very much for the invitation. It is really a pleasure and an honor to be here today. While we are getting the slides up, I would also like to congratulate Dr. Collins on the first half of his career. Well done.

While we are getting geared up again, I thought it might be useful to remind you that all human disease has a genetic component. I think we tend to forget that sometimes. On the one side, we have monogenic disease, where a broken gene causes the disease. There is no environmental component.

On the other side of the spectrum we have trauma, if you will, or infectious disease. But even those have genetic drivers with respect to healing and interactions with a pathogen.

The original vision of Navigenics was to, early in life, completely articulate your entire germ line genetic risk for all human diseases and then, across your life span, unmask portions of that information that may be useful within that window of life and then use that information in conjunction with a physician to either avoid environmental stimuli that might kick off that complex genetic disease and put that person on a focused biomarker monitoring program.

You could envision a serum biomarker for cancer at its earliest stages that you could ascertain if you knew an individual was genetically loaded. Ultimately, [you could] either put someone on a primary prevention therapy or treat the disease early so that you could reduce the burden of disease for that individual but also do that on a public health level.

I should mention I was trained in a public health department. I also trained with genetic counselors for the first two years of my career. So I come from a monogenic testing background. What I would like to do in these 10 minutes is perhaps convince you that what we are talking about today is not so different from what we have been doing for the last 20 years in the field of medical genetics.

For the first 15 years of my career I was involved in doing linkage analysis to identify broken genes that definitively cause disease. We have been successful in doing that. We have identified

the genetic basis of about a dozen monogenic diseases. Those were really easy to find homes for, meaning you could toss a mutation across the fence to a molecular genetics testing facility and have it adopted. We had medical geneticists who knew how to interpret that information. You have the mutation and the loss of function mutation with a penetrance metric associated with it, and this is what is going to happen to you, your unborn child, or your planned children.

We have that entire infrastructure, but we didn't at one time. We didn't have that infrastructure. There were no genetic counselors at one time, and it is recent history.

Now that we are doing medical resequencing of genes in people who are unaffected, we are starting to understand that penetrance in itself is a concept that is going to be modified dramatically moving forward. As we start doing whole genome resequencing in unaffected individuals, we are going to be turning up people that are compound heterozygotes for mutations that don't have a phenotype. What does that mean in the context of traditional medical genetics and genetic counseling. That field that we understand as set in stone is evolving as well.

What I would like to posit is that alleles of "low effect size," of odds ratios between one and 10, are not so different than monogenic mutations with penetrance variables associated with them.

But before I get into that, I would like to, over the course of the next, I guess, eight minutes, communicate to you that we are facing a healthcare crisis in this generation. We don't want to underestimate that because I believe that that should be the primary motivator for all of us. We are on the trajectory; I think everyone would agree. The key driver of mitigating that crisis is going to be prevention, I believe. If you believe that, then we should use all of our pre-symptomatic risk information to maximize our ability to focus our prevention efforts and improve outcomes across the population.

"Genetic risk factors" is a term that I really like because it embeds all of our understanding of environmental risk factors into what we are going to be talking about today. They are not so different, genetic risk factors and environmental risk factors.

These genetic risk factors can be used to refine risk in a clinical setting in addition to other types of risk factors. We need a new delivery vehicle for these types of genetic risk factors. You can look at someone and say they are obese or they smoke. You can't look at someone and say they harbor a 9P risk variant, and you can't place that type of genetic testing into the traditional monogenic testing environment because it is not geared to do that.

We have done a lot of monogenic disease identification, and here are a couple of examples. We have also, in my group, identified the alleles that drive several dozen common complex genetic disorders. This was a paper we published in Science. It was the first paper that used over 500,000 SNPs to paint the genome and identify chunks of the genome that co-segregated with disease or were enriched in people with diseases versus without diseases. We went on to continue to flesh out the Alzheimer's story with another allele that seems to be withstanding replication by the community.

We do this also on a national level. I chair an NIH-funded consortium. This is funded by 15 NIH institutes. It provides these types of genome scanning and interpretive analyses for the entire scientific community, essentially. We have done over 400 projects. Many of those are whole genome association studies.

The point here is that we come from an understanding of the technical nuances from which this information is derived.

I just couldn't stomach going out and raising another $1- or $2 million to do another one of these whole genome association studies without an implementation infrastructure waiting on the back end. It seemed like a frivolous exercise to me.

Now, don't get me wrong. On the therapeutic side this is incredibly useful information. But on the risk assessment side there was no infrastructure. So I have taken a sabbatical from TGen to found Navigenics, along with David Agus, to understand how we can use this hard-wired risk information to alter the natural course of common chronic diseases so that we don't see these explosive rises that are anticipated. This happens to be Alzheimer's disease, but this same curve can be drawn for any of the common chronic age-related diseases.

Really, the only way to alter the course of this massive trajectory, looking at millions of people costing the healthcare system trillions of dollars, is through early detection and preventive strategies. This vision came about that I already articulated where we get a genomic sample early in life, we fully sequence the genome for both common and rare variants, and de novo variants, do holistic copy number analysis, sift through all of the epigenetic modifications and sequence the mitochondrial genome, and push all of that information together.

Remember, we are building the infrastructure to do this. The interpretation doesn't exist yet for the vast majority of these.

Then we would] put all of that into a big computer and push a button and get a rank-ordered list of your predispositions that you can then practice preventive medicine around.

Now, for a few common complex conditions the information does exist and is robust. I would posit for, for example, disorders like age-related macular degeneration, hemochromatosis, Alzheimer's disease, we have captured a significant amount of the genetic contribution and continue to do this.

But we recognized we are building a new industry, so from the very outset we understood that there were ethical concerns, there were counseling learnings that hadn't been done yet, clinical paradigm shifts, et cetera. So we really, from the very beginning, from the inception of this company over two years ago, built a gold standard team, from the board of directors to our clinical advisory board, really understanding how does medicine need to evolve or change, or should it, and how do we interface with the medical community in the appropriate way.

The scientific advisory board, folks like David Botstein, Isaac Kohane, Nick Schork, and others, are really trying to guide us through this complex science to really understand how to provide genetic counseling. This can be very important information to an individual. So we have, for example, the past two presidents of the National Society for Genetic Counselors on our taskforce.

Then, of course, policy and ethics. An important component of that is Paul Slovic, who is a risk communication expert. So, do you communicate risk as 1 percent or one over a hundred. How do you use colors. How do you use words to maximize the accuracy of the risk information that you are providing to someone.

We have also taken great pains to build a team of genetic epidemiologists in-house -- so, genetic epidemiologists and epidemiologists -- to vet all of the literature that comes down the pike with respect to I'm going to call this validity.

These are [what] we are calling our curation criteria, but we believe that these are more practical curation criteria than, for example, the Venice criteria because, without a loss of accuracy of significance, they allow us to really click through studies and identify what is real and what is not by fully reading those and then implementing those on our risk assessment panel.

From day one we have decided quality is of the utmost concern. I should mention that for the first year and a half of the company's existence all we did was try and understand the regulatory environment. We probably spent over $10 million just trying to understand how we would click into the established environment. We feel like we have really digested and understood how to do that.

This is an example of that. From day one we decided we needed a CLIA-certified laboratory with extremely stringent QC and QA parameters. We are measuring quality on a per-SNP basis across the population with respect to Hardy-Weinberg, equilibrium checks, et cetera.

Also, we have put a lot of effort into understanding how we use retrospective case control data -- given that this is a germ line constitutive insult, if you will -- to go from odds ratios to relative risks. We have muddled this out and we feel like we can do this fairly accurately. I can point you to our website where all of our information is fully transparent.

You have seen some of this this morning as well, but given the current common risk variants that we have, how much predictive power do we have. What you see are a bunch of ROC curves. These are all generated by downloading the primary data from Framingham and Wellcome Trust and other data sources and actually applying our algorithms onto those data sets to understand the AUCs and ROCs. These are also going to be available.

I would like to segue now into talking about, just briefly, a common argument, that these genetic effect sizes are so low you shouldn't bother with them. The genetic effect sizes that we are talking about -- odds ratios or relative risks of between one and five, let's say -- are exactly on the same scale and order of magnitude of the environmental risk factors that our public health community has commonly messaged.

The next argument is, these haven't been studied enough. If you look at some of these papers that have been published, for example the 9P variant that predisposes to myocardial infarction, that has been studied in close to 17,000 people. That is a fairly large data set. It has been replicated twice, again in data sets of a thousand individuals each.

So I would say the numbers here are often on par with environmental risk factor studies. But what you see here in black are homozygote odds ratios for the genetic risk factors that Navigenics is testing for. In gray you see the heterozygote risk effect sizes. The triangles indicate the environmental risk factors that we have culled from the literature as being valid for the common diseases we are testing. You see there are all in the range of between one and 10.

A practical example and then I will end. This is the state of the art of clinical reassessment for myocardial infarction that is practiced in the primary physician's office. The physician will test your blood pressure, probably do a cholesterol test, and ask you if you smoke, if you exercise, or if you have type II diabetes. Based on this information, generally if you have three of these

things, you go on a statin and you are told "You better be careful or you are going to have a heart attack."

Very rarely are these things plugged into the Framingham Risk Calculator. In the real world, if you have two of these you are probably going to get a heart attack. Here is a statin. If you have one of these, go home and watch yourself and be good.

But these are the effect sizes that we are talking about that are driving clinical decision-making. Now if you add in the two vetted genetic associations, you see that the effect sizes are exactly on par with this. So to say we are not going to use that information because it has the word "genetics" in it, or we are not going to use that information because there is nothing you can do about the genetic variant, I don't quite buy that argument because there are lots of things you could avoid to balance out your genetic load.

We have decided we need professional access to counselors and physicians. The whole reason we went DTC in the first place was a conscious decision so that we would minimize the possibility of health insurance and life insurance discrimination. Now that we have gotten GINA we are relaxing that a little bit and building out our physician channel. You will see a lot of that moving forward.

But basically, we are trying to use genetic information to motivate behavior change, and there is evidence of this being published. For example, the Reveal study shows minimal distress to people who got their E4 results. This is a wonderful study by Aspenwal, et al, that was just published that shows people who are at high risk for melanoma based on a family history then got genetic testing. Those who got genetic testing went and got screened more often than those who just had a positive family history, showing that the word "genetic" can motivate behavior change.

I will end with this slide saying that Navigenics doesn't make tools, we don't decide on what to do in the clinic after a person gets their screen done, but we believe we can digest all of the information that is in the literature accurately and provide that in a transparent and accurate way to an individual so that they can use that risk information moving forward.

I should say we will be turning on monogenic testing very shortly for hundreds of genes and the capability to capture rare variants and common variants for common disease moving forward, which hopefully will explain more of the heritability that Dr. Collins talked about.

We have ongoing clinic trials with the Mayo Clinic, for example, to understand how this information changes an individual's outlook and how best to communicate it, as well as with Boston University and Bob Greene there. So, thank you very much.

MS. AU: Thank you, Dr. Stephan.