September 2014 Issue | Jennifer Lovejoy, PhD

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Welcome to *Functional Medicine Update,* September 2014. As you know, we've been putting together a small, intensive mini-course on the nature of change of medicine, going from a disease-care focus to a healthcare and wellness focus. Big data and systems biology in medicine is going to revolutionize this transition. To understand the context of this I think we have to go back and say, "What is medicine doing today in the chronic disease area?" How is it actually managing people who have diagnoses of various chronic diseases? I think the best window of understanding to that question is to look at what drugs people are using today to manage these symptoms of chronic disease. How do they relate to the business of medicine, which is focused on these disease endpoints?

Examining Big Pharma's Role in the Treatment of Chronic Disease

It's interesting. If we go down the major Big Pharma companies and what their blockbuster drugs are, we start with the number-one-ranked pharmaceutical company in the world today, which is Novartis. Its top-selling drugs are Gleevec, and Diovan, and Lucentis. So you're talking about cancer, and you're talking about metabolic disease. Pfizer is Lyrica, which is surprisingly their number-one-selling drug now—almost four-and-a-half billion dollars of annual sales. As you know, it was approved originally for fibromyalgia syndrome and now there are other kind of chronic complaints for which it is being used. And Enbrel, at 3.7 billion annual sales for arthritis.

Then we go to Roche: Rituxan, so that's oncology, Avastin (oncology), and Herceptin (oncology). So we would say that right now, with the acquisition of Genentech by Roche, you have pretty much transitioned the company into an oncology company. Sanofi: Lantus, Plavix. Lantus, as you know, their insulin delivery system—seven-and-a-half billion dollar sales for diabetes, principally type 2 diabetes. Merck is the number five largest company, with Januvia, which as you know is a GLP-1 agonist, and Zetia for cholesterol management (a cholesterol-binding agent), and Remicade for arthritis (a TNF-alpha-blocking agent).

Then you go down to cases where you're looking at companies like Lilly with Cymbalta, and its effects on behavior and mood (antidepressants). And then number ten, is AbbVie, which is the pharmaceutical

spin-off from Abbott Laboratories, with their giant blockbuster, ten-point-six billion dollar annual revenue drug that has replaced now the statins as the number-one-selling pharmaceutical in America, and that's Humira. Humira, which as you know is another TNF-alpha-blocking agent drug/biologic for arthritis.[1]

Earlier Screening and Intervention Will Shift Focus from Disease Treatment to Wellness

So you can start seeing just from that list that the medications that are being used are really treating the end-stages of various types of chronic illness by blocking signals or modifying various endpoints in the cycle that are related to disturbances in metabolism. So what do we do if we want to move earlier in the intervention—move away from the disease-based model to the wellness-focused model? We need to screen earlier, and as you probably recognize, there is now a very strong motivation through the genomic testing and the proteomic testing. I call it the new biology in medicine—the systems biology—to start taking broader swaths of data on individuals that are not yet diagnosed with disease, so we might call them early symptomatic, or people at relative risk.

And so we go from the general concepts of risk from the Framingham study, like risk to heart disease (smoking, maleness, age after 40, obesity, diabetes, elevated cholesterol, elevated blood pressure) to more broad-based genetic risk factors and proteomic risk factors. And there is a very interesting article that appeared in the *New England Journal of Medicine*earlier in June of 2014, volume 370, page 2442, in which the authors talk about what are the criteria for screening an asymptomatic person for genetic risk to a later-stage disorder?[2]And of course, this is a very dramatically changing playing field, because we're not only now looking at diseases that are life-threatening and have serious genetic implications, like that of the BRCA1 and BRCA2 mutations that give rise to very significant increased risk to breast cancer and ovarian cancer, but we're now looking at a variety of families of genes whose SNP forms increase the relative susceptibility to virtually every one of the chronic age-related diseases, and how we use that data, and how we manage, then, patient risk in this medical environment that really rewards more crisis care and is less focused on both emphasizing and reimbursing for early-stage chronic care.

Which then leads us to the more recent article in the *New England Journal of Medicine* titled "Genotype Phenotype Correlation." The subtitle is "Promiscuity in the Era of the Next Gen Sequencing."[3] As you probably know—as we've spoken about over the last several years in *Functional Medicine Update*—we're witnessing a remarkable breakthrough in technology as it relates to the genomic sequencing and analysis. Whereas the first genome to be fully sequenced was over a billion dollars of expense (well over—more like two billion), the cost of sequencing the genome now is being driven below a thousand dollars, which makes it like a standard expensive lab test. And so we're seeing an extraordinary number of people now using the Illumina technology (the next generation genomic sequencing technology) who are having full genome sequences done in which this big data is now available for interrogation. And that is really creating a much more interesting and robust opportunity to connect together these genomic patterns that are buried within our legacy, with that of increasing risk and

incidence in the phenotype of chronic illness. And so what we're really saying is that the whole exome sequencing using this next gen technology is getting us to understand much better the correlation between our phenotype—these biomarkers that are associated with early-stage assessment of susceptibility or early-stage disturbance associated with chronic illness—and our genetic information and how that gets translated or expressed into function.

Now what is that going to do as it becomes more prevalent in medicine as a theme that will kind of bend the curve and really produce a different way that a doctor looks at their patient, and a different way that a patient has expectations for the health care that they are going to be delivered? That's this concept of promiscuity in the area of next generation sequencing that is described in the *New England Journal of Medicine* article, really saying that we don't know exactly how this is going to shape the forces and the technology and the business of medicine, but we're very sure that it will shape it. It's going to come out of collaborative studies that have been done in individuals who are not yet ill, who are on certain trajectories towards chronic illness, that you'll be able to make these genotype/phenotype correlations. And in fact that will come out of what is called the n-of-1 trial, not just the large, statistical, average, randomized, clinically controlled, placebo trial, but n-of-1 trials in which the person is a control against her- or himself.

When we talk of n-of-1, this is a clinical trial in which a single patient is the entire trial. It's a single case study, but it's being done under the principles of good data selection, good data collection, and appropriate data analysis. This trial is one in which the patient is evaluated against themselves after either the placebo or the experimental control system. This type of study has given rise to a new way of looking at the development of therapeutics, which is called patient-guided therapy, which is how you assess the dose and response in an individual patient by using their own response against themselves rather than against some average recommendation of dose-per-body-surface-area or for some other physiological group average parameter (like a number—like get the number below a certain level with a drug).

So this patient-guided therapy is really kind of more of an n-of-1 procedure. If there is an uncertainty about the specific approach or dose to use of a therapeutic, the n-of-1 trial can be very, very useful. And the n-of-1 trial is going to be extraordinarily useful in determining this genotype/phenotype correlation with an individual. So the kind of group aggregate understanding—cohort analysis, where the big data sets might emerge to be of clinical interest and not just lost in the noise of the average—can start to be seen.

The Pioneer 100 Project: Step One of an Extraordinary Longitudinal Study

And of course, this is the foundation of an extraordinary study that is now ongoing out of Seattle, Washington at the Institute for Systems Biology that you heard Dr. Lee Hood talk about, which is called the Pioneer 100 Wellness Project, in which a collection of a vast amount of data, including genomic,

proteomic, and sociobiologic data is being accumulated on a hundred apparently healthy individuals, from which, then, correlations will be made between secondary biomarkers (things that are in their phenotype) and genomic information. I've been very privileged to be a part of this project, as I've mentioned to you, from its beginning—one of the hundred participants. And we're very fortunate to have this month as our key opinion leader, the director of this program, Dr. Jennifer Lovejoy, who is going to talk about how this n-of-1 concept is embedded within this large, big data study, from which hopefully will emerge information that connects certain cohorts of genotypes together (or patterns of genes together) with certain phenotypic outcomes that relate to early understanding of chronic illness, that then intervention using lifestyle management/lifestyle medicine that is personalized to the individual can have dramatic and positive impacts upon their health outcome.

This is a very, very different strategy than a drug trial in a randomized, placebo-controlled fashion for looking at the effect against a single endpoint with a single drug. What we're really looking at here is complex interaction of the individual in their genotype with their environment to produce an outcome in their phenotype, and then how that correlates with, in this case, 99 other people who are going through similar n-of-1 experiments. A very different strategy that is going to focus on the development of a "health" care industry and not just a disease care industry. A new methodology is needed to build this health care science base, which is the discussion that we're going to engage in with Dr. Lovejoy as it relates to this Institute for Systems Biology-sponsored, Hundred-Patient Pioneer Wellness Program.

So with that as an introduction I hope you are as excited about this as I. It fits together wonderfully with the previous discussions we've had with Dr. Lee Hood, the founder and director of the Institute for Systems Biology, and Dr. Eric Schadt, who told us from the work that is being done at his institute about how systems biology is manifesting in our understanding. I think you will find this as a next step in really seeing how the tire meets the road and how it's going to bend the curve in health care. Now with that, let's turn to Dr. Lovejoy.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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We've been very, very fortunate over the last couple of years to have some extraordinary luminaries who have expanded our understanding of what this universe of health care is going to look like in the 21st century. No surprise this month again, I have to say. We're very fortunate to keep that precedent going. Dr. Jennifer Lovejoy is our expert, our key opinion leader this month. She comes with an extraordinary background. I've had the privilege of knowing Jennifer now for more than ten years, I believe. She comes with a biology background—a zoology BS from Duke University, and then on to get her Masters and ultimately her PhD in physiological psychology at Emory and then did a postdoctoral fellowship in endocrinology and metabolism at the school of medicine at Emory.

Her publication record, her teaching, her leadership I guess we would say would focus on the areas of eating, eating disorders, obesity, bariatrics, metabolic disease, lifestyle management across a wide, wide range of experiences, both as past dean of nutrition and exercise science at Bastyr University, as an executive director in the weight nutrition program for a company called Free and Clear that was ultimately acquired by Alere, where she made contributions to the development of extraordinary patient management/patient interactive programs for weight, diet, and lifestyle management and other lifestyle habits.

Most recently—and that's what leads us into this interview—a role that I'm extraordinarily interested in, not only intellectually and academically, but I'd have to say personally because I happen to be one of the participants in this program under her and her team's leadership, and that's the Hundred Person Wellness Project that's being overseen by the Institute for Systems Biology in Seattle. That name should mean something to all of you listeners, knowing that we had the privilege of interviewing Dr. Lee Hood, the founder and president of the Institute for Systems Biology. They've advanced, as you heard from Lee, this extraordinary, innovative and first-step-forward project to assemble complex data sets from a hundred individuals to really track aspects of their network of physiological function interfaced with lifestyle and their environment, diet, and tease out, then, what we really mean as "personalized" from the data that is being collected on these individuals over the period of them being tracked. As a participant in this study, I'm one of the one hundred in this initial pioneer project, which as you probably know and we'll hear more from Jennifer, leads into maybe a thousand, and then ten thousand, and ultimately a hundred thousand subjects in this 21st century Framingham study that you heard Dr. Hood talk about.

What I've learned so far…it's one of the most exhilarating and exciting ways to see a lot of what we talked about up in the blue sky of theory get translated down to the ground in terms of really how it infects individuals, and in this case the individual happens to be me and it's been really a very, very fun project to date and we'll talk more about that, both from I'm sure my personal experience but more importantly in terms of the experience of the hundred people that have been involved. Jennifer is sitting on top of this large data set.

Dr. Lovejoy, welcome to Functional Medicine Update and thank you so, so much for your time and being with us.

JL: Oh, yes. Thank you for having me. I'm very glad to be here.

JB: Let's jump right into this. You know, this is a very ambitious and exciting project to try to track this complex web of function, the interaction of genes with environment in a hundred different people. Let's talk about what gave birth to the project. How has it kind of been organized? It sounds like it almost has to be a military operation in terms of its execution to manage all the variables, here. Give us a little of the landscape as to what led into it.

Study Goal: New Metrics for Wellness that Will Revolutionize Healthcare

JL: Well, it certainly as you know evolved out of Lee Hood's vision for P4 medicine—what's really going to revolutionize and he believes democratize health care in the future. It's a huge vision and it has to start with a small pilot study, which is where the idea for this came from. The things that I think are driving this pilot for the hundred that as you say we'll ultimately take forward into the thousand and ten thousand and beyond are fascinating because it's really not only looking at the scientific discovery and the potential for the scientific discovery is just phenomenal and very, very exciting. The things that we can discover will be new metrics for wellness, which are very much needed because we don't have a whole lot of concrete metrics for wellness, early transitions to disease (much earlier than the healthcare system can detect them today), but then on the personal side, really optimizing wellness for the individual in an extremely personalized way, something that you're very passionate about, I know. That integration, I think, of the scientific vision with the personal optimizing health for an individual—really seeing life-changing stuff, and we've seen some life-changing stuff already in the study, which is so exciting. I think it is really what drives this project and what's going to carry us forward. We're learning a lot. This, in many ways, is a feasibility study, and that's how it was conceived, I think, that we just need to know who our partners are going to be in this, what vendors are we going to use, what sort of operational things and logistical things do we need to learn, as you say, for this military operation, and how do we analyze the big data. So all of those things have been a huge learning experience, but very much with the foundation that we want to change the way health care is done to make it more effective, more personalized, and more proactive.

JB: Wow. Congratulations. Let's go to the structural parts of this. How did you actually sit down and take these laudatory and expansive goals and get them designed into a program that can be implemented?

Organizing Data in Quadrants: Genetics, Microbiome, Quantified Self, and Functional Laboratory Testing

JL: Well I've been with the project since January, so I have to certainly credit the team because some of this work was done before I joined. The concept of the study started being discussed last fall, and thinking about what was actually going to be done, how we would recruit, what would go on, going through the IRB process to get it approved as a formal clinical study with the appropriate human oversight. All of that was in the works when I joined the project, but for me it is taking the huge picture and trying to figure out what are the elements that can be expressed?

So much has been done with functional medicine and the matrix, and you take this massively complex web of interactive systems and try to draw it down into its fundamentals. One way that we did that was to look at the different sectors of information, if you will—the quadrants—that we're going to be collecting data in. So we have genetic data; we're doing whole genome sequencing on everybody in the study, so not just the SNP analysis that is often done. We're looking at microbiome data, which is a very unique

and novel aspect of the project that we're just starting to get data back on now and it's very, very fun. It's obviously early science. We don't know a whole lot. There's not a whole lot of research out there to base things on, but it has been quite interesting to look at the results from that. We're doing quantified self—kind of what I call personal trait data. That's everything from having people wear a Fitbit activity monitor to tracking their weight to personality tests and medical history (family and personal medical history)—all of those things that really drive the trait or quantified aspect of it. And then we have the functional laboratory testing. We're doing a mixture of what I consider to be conventional classic laboratory testing (chem panels, that sort of thing), but also a lot more novel functional testing around, particularly, nutrition. We've very focused on nutrition in this project because obviously that is an entry way into optimizing wellness and things that tend to go wrong early on in the transition to disease often relate to a person's diet, so we're really focusing in on a lot of those nutritional variables, but a number of other things as well. So, bringing together and thinking about those four broad quadrants of data is one way to take the huge cloud of things and start to simplify it.

Then, as the data started coming in, even just with the laboratory work, which was the first data set that we got back, it was still a lot of data. It was hundreds of data points, and so I started thinking, how can we sort of organize this, just to talk about it and make sense, and for the coaches to be able to talk to participants about…you obviously can't talk about 200 or 250 data points on a single 30-minute coaching call so how are we going to narrow it down? From there I think it went for me into clusters of actionable opportunities. So we look at a cardiovascular cluster, a pre-diabetes cluster, a nutritional insufficiency cluster. Things just started to fall out as I looked at patterns in the data to say, "These things tend to cluster together." And sometimes people have more than one, sadly; we see that as well. Everyone in the study—I can say 100 percent of people in the study—had at least one actionable item just out of their lab work. One of the questions we had going in was, are we really going to find actionable stuff (this is a pretty healthy group for the most part), and the answer is yes. We are finding actionable things, and of course as we go on now with genetics and the microbiome and quantified self we're finding more and more things that we can do, so I think we can put that one to bed. Everyone can optimize their health.

JB: Yes, as a participant I can absolutely attest to that. It's been very, very illuminating for me. I just got back the gut microbiome information and it just opened up a whole new window of understanding about my own physiology. And then, of course, the other things that you mentioned. I would suggest that you have recruited, I think, probably a hundred thoughtful people about their health, so this maybe a very interesting select group of the total wash of the population. In fact, you might talk a little bit about who are these hundred? How did you recruit them? Are there any characteristics of the psychographics or demographics of this first group of pioneers?

JL: Yes, these people truly are pioneers. They are individuals who really were part of the social network of the leadership of this project (Lee and other people who have been involved with the team)—individuals that Lee and the team knew were interested, passionate, intellectually curious, and would want to be part of this, would want to be on the ground floor. Not just be part of it, but be on the ground floor. They are definitely an interesting and not really typical Main-Street-America group because we're getting their input and value from the things that they're giving us feedback on, that they're teaching us about in the project as much as the other way around and that's really part of the feasibility and operational aspect of this: What's working? What's not working? How can we take your experience as a participant (for these hundred people) and really apply that to be able to grow the project the way we want to in a better way going forward. We were looking for people that we knew would not hesitate to give us that sort of

feedback.

JB: You mentioned the complex array of data points. How many data points do you estimate your project will ultimately acquire, just to give our audience some sense as to what we mean by big data?

So Much Data: How Much is Appropriate to Share with Patients?

JL: Well, we know there are billions of data points just in the genome alone, so we're definitely in the billions. We're doing metabolomics, so that's up in the thousands. Proteomics, which can obviously expand also quite large into the thousands. It's very big. It's well into the billions. Now, obviously again we're not sharing all of that information. We can't share all of that information with individuals because what would you possibly do with it? Even a hundred data points is overwhelming for an individual, which is really where the behavioral coaching becomes so key, and the clinical oversight. And we do have a study physician that we're working with. We have a medical advisory board that is helping us to really think about this clinically and behaviorally: how do you give the most appropriate information? How do you help people to prioritize the information that is most likely to optimize their health?

The excitement about big data is on the analytic side. Really as our analytics team starts diving in to the much larger data sets than just the top layer that we're right now sharing with participants, that's where the discoveries are going to come from and ultimately those may be things that we share with participants. We might find a new variant that is very important for wellness—that might be a wellness metric, or we might find something in the metabolomics that links with a blood value and all of a sudden we've got something that's really a new story that we can tell people that's going to come up in priority, compared to where it might be today when we just don't have the data to back up talking about it. The big data aspect of it is definitely very central to what we're doing.

JB: So I think this is a really new science method. I hope our listeners are catching this because in the past we always think about the randomized, double-blind, placebo-controlled trial. This is an n-of-1-type study, but—by the amassing of many n-of-1s—it has a group effect that gives other opportunities for discovery that you would not have anticipated, so you're getting a twofer, basically. The twofer is, number one, you're giving personal information of that person against themselves as a control, and number two, you're aggregating all of these n-of-1 data to create the opportunity to discover cluster, as you pointed out, that might emerge as dominant themes that would allow us to take an overwhelming amount of data and get it down into buckets that are manageable in terms of aggregate group cohort intervention. I think this is very different than a traditional type of drug trial or epidemiological survey. Was this part of your design from the very beginning? Because it's even a little different than Framingham in that respect, I believe.

New Statistical Techniques Needed for n-of-1 Trials

JL: Oh yes, absolutely. And I have to say that it was a new one for me. I had spent my entire research career doing randomized clinical trials or classic observational epidemiologic studies, so the idea of an n-of-1 trial was new and not something that I had really given a lot of thought about, and part of the audacious vision, I think, of this is we not only have to integrate and develop the medicine and the practical applications, but a lot of the statistical techniques that are going to be needed in order to do this type of n-of-1 trial need to be developed and will be developed, I'm sure, by leading thinkers in that field.

That's a piece of it that is needed as well.

I think for me it just made fantastic sense to approach it this way. Having done clinical trials, the notion that taking a large population, randomly assigning them, and then looking at aggregate average responses of the population…it tells you something—I mean, it's not completely without value—but to really get at the kind of personalized medicine and optimized wellness that we want to get to, it's not going to get us there. I had directly experienced this in many cases in my own clinical trials that I conducted earlier in my career, where there was always one or two or three or more outliers that just didn't behave the way the rest of the population did, and that's fascinating. Those were always the ones who were the most interesting: why did this happen? And that's true for behavioral trials and lifestyle trials as well as drug trials, where obviously that's been clearly shown in many kinds of drug trials. I did primarily more behavioral and lifestyle trials, but you still see it—people who don't respond to a lifestyle intervention, or respond in a completely opposite way. You can have people exercise—I was talking to someone about this the other day—and their V02 max actually gets worse based on their genetic profile and other things. So thinking about those sorts of things and trying to consider doing that as an aggregate measure in a clinical trial, I really understand the benefit of this approach and really trying to move medicine forward.

JB: Let me talk about one things learned, and this is going to seem, probably, like a "duh" to you being an expert in physiological psychology and the whole nature of how the mind and the body interface. So my observation was wearing the FitBit and doing this telemetry with blood pressure management is kind of a real-time, 24/7, reinforcement of your engagement with your health. Even if the information in and of itself is not always exactly practical, it introduces you to your function in a different way and makes it very intimate and sentient. It's not like somebody else's data. It becomes your life, your response. If we could do continuous glucose monitoring, that would be like wow. You would know every stress and how it affected your endocrine system. Have you seen this as a general theme in the participants when they start measuring these things in real time on themselves?

Wearable Technology: Accountability Appears to Drive Motivation

JL: Absolutely, and it tends to kind of build. It builds motivation and then people want to track more things. The FitBit has been really well-received (just doing that sort of tracking). People find that it keeps them accountable, which is very important, because it's right there—you're looking at it, you're seeing how many steps, how many minutes of activity you're getting, how much sleep you're getting, if that's an area that you're working on. That accountability is often what drives motivation and then as you say it is reinforcing. When you have a good day—when you get your 10,000 steps—you feel good at the end of the day because there's that sense of accomplishment about it.

I think it really is that sort of reinforcement and accountability that honestly drives the quantified self movement in general—that people just start getting so fascinated about tracking these aspects of themselves. And the more they can do that and get the detailed sort of thing, I think in the future we are going to have the kind of devices that can measure not only blood glucose, but give us continuous heart rate monitoring, we can look at heart rate variability, which is an area I'm very interested in, and other things that we'll have the technology to do that we don't quite have today, but then I think it will really take off even more. Just what we have right now, with a very basic monitor, is giving us some great accountability and motivation for people.

JB: Have you found any pushback at all at this point? Now again, we have to contextualize this—that these hundred pioneer people are maybe uniquely self-motivated—but is there any kind of feedback you have gotten of "Well, this is too much work" or "I really didn't want to know that much about myself" or "Gee whiz, it's easier just to wait until something happens before I do anything about it." What kind of feedback have you gotten on that side of the equation?

Engagement is Variable, Even in a Compliant Study Group

JL: Yes, by and large this is a pretty compliant, pretty engaged group compared to an average clinical trial. But that being said, we do have somewhere between maybe ten to twenty percent of the group that is just not particularly engaged. They are not particularly doing anything. They might have shown up for their baseline blood draw, but we're having a hard time connecting with them beyond that. So there is variation, even within this group, in terms of their engagement in the project.

The other thing on the flip side of that that has been very fun to see is that we had people who at the start of the project, as far as they knew they were healthy, and their goal for really joining the project (that they told the coach on the first call) was "I'm just curious." So they didn't particularly have any sort of motivation about actually changing lifestyle, changing health. That all changed when they got their first set of bloodwork back and the coach could actually talk to them about variables that were not perhaps in range, that might be leading to something, and it was like flipping a switch in people just to say "Wow. I didn't think I had anything to work on. Now I see that I really do and that I can be healthier," and so they are very, very motivated, and that's been a lot of fun.

JB: So let's talk a little bit about your coaches because I think this is a very important part of the human side of this whole concept. I think you have done a tremendous job. Sandy is a brilliant coach. Tell us a little bit about how you selected those people, what your expectations are for them, and what they have learned so far as it relates to their engagement with participants.

Coaching is Key in a Study on Lifestyle Change

JL: It's a great question, and I have to say that Sandy, for the hundred, is our only coach. We have one coach and she has done just an absolutely amazing job. Sandy's background is she is a registered dietitian. She also has a pretty broad base of knowledge of functional medicine coming in; she was trained at Bastyr. We had a lot of discussion early on about who should the coaches be for this project? Should we go with Bachelor's level kind of lay health coaches, which is what we did at Free and Clear? Or should we use nurses, should we use naturopathic doctors? I mean, we really discussed the whole gamut of what would be optimal background in terms of the coaching. We settled on registered dietitians. We're feeling pretty good at this point about that decision because of the emphasis on nutrition and the ability that dietitians have to coach to a broad set of lifestyle change.

We're not practicing medicine, and we don't want to do anything that might appear to cross the line of practicing medicine, so it really is about lifestyle, it's about health education, but with the sophisticated knowledge that a highly trained registered dietitian brings to the mix. How we're going to scale that going forward is something that we're having active discussions about (what we might do from here on out). It is an awful lot of information, and it takes a very special person—a very sophisticated person—to be able to integrate not just lab value, which most RDs are obviously used to working with, but getting into

gut microbiome and genetics, which is fairly foreign to many allied health folks anyway, and MDs as well honestly. I mean, it's just not an area that's very familiar to people. That's one of the big discussions we're having right now, about how do we scale that? But I think that choosing to use RDs as a coach was a really good way to go.

JB: Well, and she—as you said—is very special in her broad-based understanding of the connection among many of these buckets. Let's talk about the buckets, here, for a second. I'd like to get maybe, for our listeners, a little more granular. You talked about the four sectors, so let's start with genomics and the new next gen analyses. Tell us about how you approach this concept of genomic evaluation and where you think the greatest richness will be, at least at this time in our understanding, for clinical payoff.

JL: How do we take this huge thing and organize it into logical patterns that we can actually coach to? We have three broad areas. We're looking at medical genetics and we're using the American College of Medical Genomics and Genetics list of 56 genes, so that's the serious inherited genes conditions, but the ones ACMG says, "These are medically actionable and people should know if they have these." So that's our medical genetics side. We're looking at pharmacogenomics, so that is how your genetics influences your response to drugs, and we have about 35 genes that we're going to be reporting to people on, mostly focusing on drugs that are more commonly used. That definitely will be valuable, I think, for people to know about their response in case those things come up.

But the area that I think is going to be the most fruitful and the most interesting is what I'm calling behavioral genetics. This is really the nutrigenomics. It's your response to nutrients, your ability to absorb and metabolize nutrients, so things like your vitamin D receptor status. If you have variants there we know that you don't absorb vitamin D as well. If you have a variant in the MTHFR that regulates folate absorption, we know that is something that is very common and very actionable. We have a number of genes, there, that relate to a number of areas that will be very familiar to listeners, I'm sure: detox, and absorption, and so forth. That's going to be big.

We're also looking at genes that impact the response to exercise, so we can tell people, in a broad-based way, whether their genetic propensity leads them more towards being an endurance, kind of aerobic, type athlete versus a power or strength athlete and how they can use that in their own training to motivate them.

And then lastly we're looking at weight loss, genes that impact obesity and the ability to lose weight, and the response to diet from a weight loss perspective, which is an area that, with my obesity research background, is of considerable interest and I think the science has really come along far enough that we can begin to make some ideas there that get away from the kind of hit-or-miss approach that we currently take with weight loss diets of, you know, "Well, try this. If that doesn't work, try this. Low carb. Do whatever." This is really going to say, "Your genes say you're most likely to have a beneficial weight loss response to this type of diet, so let's start there." There still may be personal or other biological variables that impact your response to it and it may not always work a 100 percent for everyone, but we think we've got a much better shot and I'm very excited to see how that plays out in our study.

JB: That's really exciting. So when you assemble this information, clearly this is another example of picking a little window of clinical usefulness out of this broad array of data, for which, once this data has been collected on the whole genome, you can come back and reassess that information as time moves

forward with new advancing knowledge. It's a one shot; you don't need to have multiple lab tests over the course of your whole life, so it's like the universal lab test (to have your genome sequenced). When people ask you about this, how do you communicate that? Because that information will be in the database forever, presumably. If they say, "I don't really want all my information to be known to the world," how are you handling the privileged information?

JL: Right. It is a huge, huge part of it, and probably the area, when we were recruiting people for the study, that there was the most concern about, was the genetic information. So we've taken a lot of steps, both in terms of the electronic security as well as personal security. Pretty much once people enter the study they are known to us as a seven-digit number, which sounds rather cold and impersonal, but as far as from a data perspective that's really the safest way to do it—that we distance any personally identifying information and everything gets analyzed and reviewed in terms of an ID number that cannot be linked back, at least electronically, to the data. And obviously the coaches know who they are talking to and what they are doing there, but that has been a big issue.

The other thing that we're doing…I mentioned the different types of genetic data that we're talking about. Everyone is going to get their behavioral genetics and their pharmacogenomics data, but people will have a choice of whether or not they want to receive their medical genetic information. We know already that some of our participants just don't want to know. If they have inherited a risk for a really serious disease, they don't want to know. So we are giving people the ability up front to either opt-in or opt-out of receiving the medical genetic data. And we're even getting a little bit more granular than that because we know that there are a couple conditions in particular that people are worried about: breast cancer (the BRCA genes); the Alzheimer's risk, which is really more of an association, it's not a single gene inheritance like BRCA; and Parkinson's disease risk. People could opt in to all of the medical genetics except for those three, or they can take it all, or they can take none of it, so that's how we're kind of handling people's concern about getting information.

I don't feel that there is anything in the behavioral genetics or pharmacogenetics that is going to upset anybody, so we're just saying you're going to get that and it's probably going to be really enlightening and really interesting, and hopefully fun to see, you know, "Wow, I had no idea that this was going on." But the medical stuff we get can be psychologically pretty challenging for people and some people may just not want it, so we're giving them that choice in the study.

Microbiome Analysis: Determining Actions Based on Diversity Score

JB: Very, very wise, I think. So let's move to bucket two, which is the microbiome. As I said, I just had a chance to evaluate my own data. I think it's very nice, the way that this data is being done. This is not a full microbiome sequencing. It's more speciation, so you're looking at the Bacteroides and the Firmicutes and other families of bacteria, and the way that the data is presented I really thought was very good because your data from your own sample is presented in the context of everybody else's in nomogram (not obviously naming people, but you can pick out your data in the sea of other people's data), so you kind of get a sense as to how you fit into that community of those other 99 people, and it also allows you to see what species diversity you have in your microbiome and also the ratio of Bacteroides to Firmicutes, which is emerging more and more from the literature to maybe be a risk factor for various steps of metabolic disturbances. How are you handling this, because this for most people is probably a very new concept?

JL: It's very new, and of course the science—what we can say about it—is fairly limited because there haven't been a whole lot of studies done on it. We are focusing, in terms of the actionability part of it, primarily on the diversity score, which is an indication of essentially how many different species of bugs you have in your gut. And so what is really consistent in the literature, even at this point, is that low diversity is bad. No matter what health condition, what metabolic condition, whatever you're looking at—if you don't have a richness of…the target I would say is probably somewhere between a thousand and twelve hundred (at least) different species in your gut, it's almost like you don't have the resilience, environmentally, to deal with what might be coming to you in your lifestyle, whether that's an illness, whether it's a drug, whether it's a dietary change—that lack of diversity seems to really raise the propensity to illness.

We are focusing in our coaching on individuals who have a low diversity score and looking at ways that they can improve that, and there are two main ways. One is to really shift the emphasis to a plant-based diet. The bugs in the gut really love plants, and that's really going to help to improve the diversity. And then we're also recommending a prebiotic supplement to help the beneficial bacteria to really take hold and to build that diversity because that's also been shown, at least in randomized trials, to help to increase diversity. We're focusing there.

The Bacteroides and Firmicutes ratio is a little bit too conflicting right now in the literature to say a whole lot about should you be trying to boost one or the other? The one "ah-ha" for me was looking at the hundred people and how big a range it was even though these are folks who are fairly similar in terms of lifestyle and diet and where they live and so forth. We have a huge range in that ratio of those two predominant families, so that was quite an interesting thing. We have seen a couple of interesting things around the families, though, which is that apart from those two primary ones that were looking at the ratio, there's a couple of minor ones that show up sometimes, and in people who have those we found one individual who had a high proportion of bacteria that are associated with inflammation (research has shown that it is associated with inflammation), and it turned out that this particular person has very high inflammatory markers in the blood and had no idea why. Great lifestyle, great diet, slim, no inflammatory processes going, and so when the coach was first talking to her about her blood results and they were talking about the inflammation and had no idea what was going on (and neither did her doctor have any idea what may be going on), and then we found these high levels of proinflammatory bacteria in the gut microbiome. Now, obviously n-of-1. We can't draw a firm conclusion about that, but I think that's where we're really going to start getting some interesting clues from the microbiome data in particular.

JB: That's really exciting. Talk about getting into the systems biology concept of health and wellness. That's really exciting. So let's move next to the quantified self bucket because that can be huge. That can be very expansive. Tell us a little bit about how you're collecting that data and what you're doing with it.

JL: We have a mix of questionnaire data. We have the personality tests, the medical history, and those are very important, certainly on the analytic side because we think those are going to be important predictors of things long term. But on the coaching side, the personality questionnaires, in particular, have been helpful too, so that the coaches can kind of tailor their discussions with people based on what they are most likely to be behaviorally responsive to. So that has been good.

And we're tracking changes over time in things that are just going on. You know, "Did you get a cold?" "Did you travel?" We had someone who went to Africa for six weeks. So those things potentially can

have a very big impact on the things as we are measuring them every three months and looking at fairly short term changes in measures. And then we've talked a bit about the activity tracker and how that is monitoring the activity and sleep, giving us feedback and giving participants immediate feedback on how they are doing it. We're using that in the coaching calls primarily when we see that someone perhaps could benefit from, say, more activity, and the tracking data that we are collecting clearly shows that they're not getting very much activity, and so the coach can weave that in to other things if their blood sugar is high, or whatever it might be, to talk about the benefits of perhaps getting a little bit more and looking at it over time. And then you have your own accountability because you can see it yourself, too.

JB: So that takes us to the fourth bucket. As I have read recently, there are now expected to be in excess of 25,000 biomarkers that people have done some work on. Clearly that's an overwhelming number. What did you select out of that wide array of things that you wanted to look at and some of these functional, maybe nontraditional tests?

The Value of a Broad Nutrition Blood Panel

JL: We're doing a broad nutrition panel that looks at both urinary markers of nutritional metabolites as well as blood markers of metabolites, of actual nutrient values of environmental toxins. I wish we had more of an environmental toxin screen, but we were taking too much blood. We had to cut back. We couldn't do everything we wanted to do. I think that is definitely giving us a lot of information and that panel alone is, I would think, over a hundred different values that we're getting out of that. We're doing a fairly deep metabolic syndrome panel that includes the inflammatory markers as well as measures of leptin, insulin, adiponectin, glucose, and so forth. That's giving us some very rich information and we do see that about 35 percent of individuals are actually prediabetic in the study, so we're finding some good things in that panel, and the inflammation, of course, is such a fascinating area and very hot topic that we're now linking to all kinds of other things and so that's providing some rich information for us.

JB: And when I looked at my own data I thought it was very, very fascinating to see the interrelationships between things like heavy metal analysis and some of your parameters relating to your fractionated lipids because you're doing nontraditional lipid gradient evaluations, which I think is very helpful (particle number and so forth), and also looking at the interrelationship that has with some of these more sophisticated markers of fatty acid composition because you have also done a very nice laboratory detailing of fatty acid intake. There are some patterns, I'm sure, that will emerge out of the interrelationship of those variables.

JL: Absolutely, and we're also doing four-point salivary cortisol and DHEA to look at the adrenal axis and that has been very interesting to relate to other parameters as well as just to look at in individuals who, again, may be fairly healthy in general but have some abnormalities in their diurnal pattern of cortisol or have relatively low DHA for their age.

JB: So clearly we could spend a day, I'm sure, and you'd still have much more to say about this program, but I hope this is going to be a point on the curve of us checking in with you as you move forward, because this is going to be an "ah-ha" experience both for you as a leader in the group, but also for the individuals within the group. There are going to be all sorts of "ah-has" down this path over the months to come. So if you were to grab your sound byte, and I'm sure you give many talks about this and people want to know what's the bottom line, how do you summarize where you are in your discovery? Do you

feel that the effort is worthwhile? Do you feel that the pilot study is starting to obviate the value of this kind of work? Do you think it will ultimately help us to engage in a 21st century Framingham that will be focused on personalized biometrics? What's your takeaway?

JL: Absolutely. I would say that we are in the very, very early stages, and that we're just beginning. So last night, we just started getting genomic data back, and I started to look at related individuals who had similar family histories but came out with very, very different recommendations from a personalized lifestyle approach to what you would do based on the genetic variants they had, their bloodwork, their BMI, and their self-tracking information. So it was the first time that I had personally been able to take things from multiple quadrants and really start to tie it together in a way that let me see how powerful this is going to be for people, and we're just beginning to get there. I think this is going to grow. We're going to learn more and more as we go on, and I have absolutely no doubts that it is going to really change the way we practice medicine and the way we do science.

JB: We know that the system that we call the healthcare system, which is economically modeled, is really a disease-care system. The incentives are all around disease care. We take some of the brightest minds of women and men and we train them to become really good disease diagnosticians and treatment agents and we build infrastructures around disease. And by the way, I'm not saying that this is wrong. I'm just saying that this is the focus that we have seen over the last 70 or 80 years in the development of the medical-industrial complex; it's focused on disease. Now we're starting to witness, through this work, the potential infrastructure based upon a quantifiable science that would be a health-focused industry. So we would have some balance between the professionality of disease care with the professionality of health care. Do you think that this will create an economic transition in emerging new businesses, similar to what we saw happen with, say, Microsoft and Apple as we went into to the age of personal computing, in which prior to that people said, "Who wants to have a personal computer? I mean, that's like for IBM to do."? Do you see some analogy, here, as to what this data will spawn in terms of transition in business?

JL: Absolutely, and that really is a huge part of Lee's vision as well, that the future of the business of health care is really going to be much more focused on wellness and on prevention and that the economics of it will be more driven by that and much less driven by the disease care that we have today. I think everyone sees that the healthcare system is broken. We just can't keep focusing on disease. I saw a report from the CDC that 40 percent of Americans are predicted to develop type 2 diabetes, now, and that kind of thing cannot be sustained in the healthcare system we have today. We have to prevent. We have to focus on wellness, and I think that's where the economic growth is really going to be in the future.

JB: Well maybe a good close would be to turn the tables around here for a second and ask you, is there anything you'd like to ask me as a participant in your extraordinary project? Anything that I—as a person who has really valued from watching how this all works at the personal level—might share with you?

JL: Yes, so can I get two quick ones?

JB: Sure.

JL: First, have you had any "ah-ha" moments from the data that you have gotten so far (and I realize it's only a piece of the data, we haven't really hit all the quadrants yet)? And then, what motivates you to stay engaged with behavior change and a big data project like this?

JB: Yes, I think number one, the answer is yes. You know, I probably have had a little bit of a benefit that most of the Pioneer 100 people probably have not, and that is I have been able—because of having a laboratory—to do, every six months, my own blood chemistries for the last 15 years. So I had a pretty good trajectory of understanding of a whole series of secondary biomarkers as to where the aging Jeff Bland was going. But I have to say that coupling that together now with the other things that you have done, and for me, although most of this information was familiar at some intellectual level, to personalize it and start seeing it as my information—this is once again the n-of-1—has really helped me to focus more tightly in on things like managing stress, which I think has been a very interesting personal discovery because I can see how my variables are influenced by the warp and weft of the life that I select to lead. So I think that that has really been a very, very good "ah-ha" lesson reminding me that we're living in real time. Our physiology is responding in real time, and it's not just the big variables; it's the small stuff that gives rise to the big stuff. I think that has been a very, personally, maybe reemphasized story. You know, a number of years ago, I actually gave, at one of the IFM meetings, my whole blood profile to the audience, before and after. A lot of people were very alarmed that I would be so audacious as to show my own stuff up there, but I found that it was actually very empowering for me to show my before and after, after I had gone through a six month program. And I think this program that you're orchestrating here is really the next step up. More information produces more knowledge which produces more opportunity for action. So that would be my long-winded response to question one.

Question two—the reason that I think I continue to be ever increasingly excited, is not only because like many people that volunteer for research projects because they want to help science and the want to help discovery, which I believe will occur out of this data set, but they also really are just very intrigued about how their bodies are operating in time, right? Having been in this field over 40 years and watched its evolution from Roger Williams and the concept of biochemical individuality to Linus Pauling with the orthomolecular concept of disease, I really see these are fulfillments of a lot of what our pioneers were speaking about 50, 60, 70 years ago, even going back to Archibald Garrod at the turn of the last century who was the discoverer of the first inborn error of metabolic disease. He talked about "in the future" maybe we would see this kind of thing occurring. So this is a little Watson and Crick-ish. This is really a transformational moment in the history of knowledge and how it can impact on people's health and wellness. It's almost like a calling. It's really, really for me extraordinary to be a participant and I just feel very fortunate to be part of your 100, so that keeps me engaged.

JL: Great. Well, we're delighted that you are part of it.

JB: Thank you.

I want to thank all of you on behalf of the functional medicine community and what we've been trying to do in Functional Medicine Update for 33 years. This is the embodiment of that, and I think it follows so nicely. Lee Hood's discussion with us and then talking with Eric Schadt about the fact that you need to go beyond GWAS to really understand this phenotype/genotype connection, and now into this, which is where the tire meets the road for individuals.

Jennifer, thank you and you're an eloquent spokesman for your project. I can see it's in great hands. We look forward to checking in with you months in the future to see how things are evolving. Thanks a million.

JL: Thank you.

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