October 2013 Issue | Michael Snyder, PhD Stanford University

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Welcome to *Functional Medicine Update* for October 2013. Boy, do we have something in store for you this month. You know, we've been talking a lot about what I call the trilogy of 'omics: genomics, proteomics, and metabolomics, which then regulates phenomics (or the phenotype of the individual). We've spoken around this. We've had many investigators and researchers and people who are very much specialists in this area talk through the landscape that defines the 'omics revolution that we're now engaged in. But never before—until this issue, October 2013—have we had someone that has the background of Dr. Michael Snyder, Chairman of the Genetics Department at Stanford University, who I think is going to open up this topic of personalized health care, personalized medicine, personalized lifestyle medicine and functional medicine in ways that may blow your mind, to use a vernacular. I think you're going to find this an extraordinary journey that we'll be taking with Dr. Snyder over the next 30 minutes. So without further ado let's jump right into out adventure with Dr. Michael Snyder.

INTERVIEW TRANSCRIPT

Researcher of the Month

Michael Snyder, PhD
Professor and Chair of Genetics
Director, Stanford Center for Genomics and Personalized Medicine
Stanford University
Palo Alto, CA
http://snyderlab.stanford.edu/home.html

This month again we're so privileged to have an individual who frames the epitome of what we're trying to get to in this clinician/researcher of the month component, which is someone really doing cutting edge work, changing the knowledge base, pushing our understanding of disease prevalence and maybe ways to modify disease expression at the genomic level at that frontier, and that's Dr. Michael Snyder. Dr. Snyder is the Chair of the Department of Genetics at Stanford University School of Medicine. He's also the Director of the Center for Genomics and Personalized Medicine at Stanford. He came from Yale, where he was in the Department of Biology there (now, Molecular and Cellular Developmental Biology at Yale), and made the transfer over to the west to Stanford. He's a chemist by training (both a biologist and a chemist). I would have to say he's probably a master of many things, doing his PhD work at Cal Tech in the Department of Biology. Again, we all find ourselves having some intellectual consanguinity; my work with Linus Pauling over the last few years of his life as a Research Director at his Institute and my vicarious connection to Cal Tech always reminds me Cal Tech graduates are individuals who have special training in translational science and Dr. Snyder has certainly brought that to his work at Stanford.

His topic is one that clearly is on all of our minds, and that is how does this genomic explosion of revolutionary information impact medicine and health care, and how is it going to find a way to converge with all the other things that are happening in information science and big data to really create a frame shift in how we understand the origin of disease, how it can be prevented, and how it can be personalized in its treatment. He gave a presentation at a meeting that I went to in Mountain View earlier in 2013, which was on personalized medicine. His talk was very, very interesting because it was a little bit of a personal history as to how genomic data could be used actually by him, himself, in constructing his own trajectory as it pertains to health and health outcome. So it was all the way from the very precise research-based information to where we start personalizing it and understanding how this can be applied in a translational way.

Dr. Snyder, we're so privileged to have you as our guest for Functional Medicine Update. I guess the first question I might ask you just to get started is, as you have made this transition from Yale over to Stanford and you've watched how the genomic discoveries of the turn of the century have started to translate into medicine, how is it seen by you? How has this directed your career and your focus as a leader in the field?

Genome Sequencing Technology Has Driven the Personalized Medicine Field

MS: Well, I've always been interested in understanding things at a more global level. I should say, first of all, thank you very much for having me on the show. The way it has affected me most is I think that we've been very interested in understanding things on a much more comprehensive level, and the genomic revolution has really made that possible. So, I think this had been happening with micro-arrays, initially, and such for being able to follow gene expression, but what has really driven the field forward I'd say in the last 10 years or so is the new high-throughput sequencing technologies that have emerged, making it now possible to characterize whole genomes at an accuracy that can be useful for clinical purposes in the so-called personalized medicine field. It's really the genome sequencing technology that has driven a lot of this, although other technologies have advanced the field as well and some of those we're now bringing to bear, as I can talk about a little bit later.

JB: I'd like to have you describe a little bit for our listeners this concept that seems to have emerged over the last 20 years where we went from discussing certain things within the genome that were not coding, which we called "junk" DNA, to where we're now talking about them as having regulatory and functional value, and how this has to do with things that regulate gene expression. It seems like this is a pretty interesting part of the development of our knowledge base.

Explaining DNA Coding Within the Genome

MS: Sure. Basically your DNA, if you will, is a giant ocean. It has six billion bases (that is, six billion letters) that define the genetic code for all of your genes and producing, basically, what you are. What we do know is that the gene part of it—the part that actually winds up encoding for RNAs and later encode for proteins—is really only a few percent, probably on the order of about one-and-a-half percent of the genome encodes genes that make proteins, and a little bit more encodes RNAs that don't make proteins. It's still a very small fraction of the giant ocean of DNA that's in our genome. One of the things that has become clear over the last, I'd say, probably 10 years or so as people started looking at this DNA that was not coding proteins, people have come to realize that it does have a lot of other things. It has, first of all, a lot of regulatory RNAs, so genes that encode regulatory RNAs. But perhaps most surprising is it has

a lot of the control elements—the regulatory sequences, or switches, if you will—that control the expression of our genes. I think what is kind of fascinating about this whole part is that the amount of information that controls your gene is probably more than the gene itself. So the switches that decide when genes are turned on or turned off or how much of a gene is expressed in each tissue are really just getting mapped out now, although there is a long ways to go. I would argue we're just getting started at it. But these switches are very, very important because a lot of the things that make people different…it's not the genes themselves, but it's the control sequences for the genes and it's something we really need to understand in order to be able to understand why people are different from one another, and actually why we're even different from our most closely related species. We think the difference between chimpanzees and humans, in fact, is mostly due to gene regulation more than to the genes themselves.

JB: You know, I just had the chance to read in the last few days, this really wonderful paper that you and your colleagues authored that appeared in the Proceedings of the National Academy of Sciences this year titled, "Systematic Functional Regulatory Assessment of Disease-Associated Variance."[1] This kind of ties together the SNPs—the Single Nucleotide Polymorphism variations—from person to person together with regulatory assessment, and I like the term "functional," how they actually function in translating into disease patterns. Could you tell us a little bit about that paper, because I think it is a very powerful story?

How Does Regulatory Information in the Genome Relate to Human Disease?

MS: Sure. One of the things that our lab is very keen on is trying to understand how this regulatory information is related to human disease. These days you can sequence a person's genome, it's not so expensive, it's about $3000 US dollars to get a human genome sequenced, although the interpretation of that sequence does cost quite a bit more; it's probably on the order of about $15,000 US dollars. Even when people do this interpretation they spend virtually all of the time on the protein coding sequence of that few percent that I mentioned before, and they ignore the regulatory sequences because they just don't know how to look at them properly from a disease standpoint and from a functional standpoint. And so with the various efforts going on to map these regulatory sequences outside genes, there are these maps. In a sense they are almost like Google maps people are trying to set up, where you'll be able to have these landmark sites, and what we're trying to do is map disease phenotypes on top of those. So, with each of these elements, can they be associated with human disease? So we have been making hundreds, if not thousands, of these associations between particular diseases like cardiovascular disease or diabetes, and trying to map these onto regulatory elements—these regulatory switches. And so at the end of the day, imagine you are a clinician in an office and someday someone comes up to you with their genome sequence, we'll not only be looking at the coding sequences but we would be looking at these regulatory sequences and seeing how they might map onto disease risk, and then ultimately make some predictions about what a person should watch out for, and maybe what they should eat or not eat, based on knowing something about, again, not just the coding sequences but the regulatory sequences in their genome.

JB: I really like another one of your recent papers that you authored, which is titled "Overview of High Throughput Sequencing Technologies to Elucidate Molecular Pathways in Cardiovascular Disease" that appeared in Circulation Research in June of this year.[2] To me that's a really interesting application of what you're speaking to in a specific disease-focused area. It sounds to me like this model will cut across all the subspecialties of medicine. It's a generalized model once it is better understood for defining functional disturbances at the phenotypic level that translate back into expression patterns that are caused by altered regulation of gene expression, which then may translate back to the environment in which the

genes are being expressed—what they're being bathed in and how that influences these expression patterns.

MS: That certainly is our hope that by gaining more comprehensive understanding of these control switches—how they intersect with disease associations and then expression differences—that we will be able to make better predictions. I mean at some level this relates to my particular story, which I know you're familiar with, which is by sequencing my genome we were able to make predictions about my disease risk, and in my case one of the highest disease risks turned out to be type 2 diabetes, which in fact I did get, and we were able to catch because we had sequenced my genome. It told me I was at risk, so I was following this and actually many other molecules as well (we were following all my proteins, and RNA, and metabolites). I can envision a future like that where based on your genome sequence you'll be trying to map out these regulatory sequences, which, again, are largely ignored right now, and then the variants that lie in those (that is, your personal variants, or your personal changes that lie in regulatory sequences), and see how they associate with human disease and the expression of the genes they control, and make predictions about disease risk that would be useful clinically. That certainly is our goal. In a sense it's really very similar to the vision that was espoused in this movie Gattaca, where people were—based on their genome sequence—predicted what they're at risk for and what their fate in life should be. I'm sure many of your listeners have seen that movie. It's a very fascinating movie, and I believe that at some level this is true. One of the big pushes we're making is, again, not just to look in the coding sequences for the genes but to look in the regulatory sequences where there is probably 10 times more information than the coding sequences themselves.

JB: I'd like to go back if I could and pick up on this fascinating story on, I guess you would call it, the quantified human, which was you. You're like the n of 1 of the start of this quantified human movement with the way that you did the 'omics evaluation, going through the metabolomics, and proteomics, and genomics, and expressomics. Maybe if you could tell our listeners a little bit more about that? I thought it was a really fascinating story as to how you assembled that information and what it led you into, knowing that you had pretty good health habits and were health proactive to begin with. I thought it was fascinating.

Dr. Snyder Volunteers to Become the Quantified Human

MS: Sure. So the rationale of this project is to essentially see how you might be able to use genomics and other sorts of 'omics information and bring it into health care and personalized medicine. I think the key feature for this is we're thinking very hard about how to do this for healthy people, not just in cases of disease, so it's pretty clear—to back up a little—that genome sequencing has huge impact in cancer. Cancer is a genetic disease and if you sequence cancer material versus normal material from the same patient you can try and find the underlying genetic mutations. It's not routine yet, but it will be routine, in my opinion, in just a few years, and it will have an enormous impact; it already is. There will be other cases, too—trying to solve mysterious genetic diseases by genome sequencing, but one thing that really motivated us is, to what extent can getting your genome sequenced now have some impact on your health care? Our lab was one of the few labs that does quite a bit of genomics and also does other 'omics. Cardiomics is the study of all the proteins, transcriptomics is the study of all the RNAs and metabolics. We had worked in all these different areas. We could see with the cost of sequencing dropping that it made a lot of sense to see if we could actually start sequencing genomes and incorporate this into health care for a healthy individual. And the other thing that I think struck me that was going on at the same time

is that I was always perplexed that when you went into a doctor's office and they took blood from you and they gave you back a report, they gave you back a report on about 15 different things, and knowing that with today's technology you can measure thousands, if not tens of thousands, of molecules from a blood sample, I always felt this was woefully inadequate—that is, we're measuring so few things in a doctor's office when, if you were to measure ten thousand things, presumably you could learn a lot more.

We had been talking a little bit about this when I was at Yale, but the motivation was when I came out to Stanford that we should really see if we could explore this bringing genome sequencing and other 'omics technologies into profiling a person's health. And so just as a pilot study we actually chose me just because of the availability of being able to draw blood, and also the fact that at the time it was a bit controversial. A lot of people were kind of scared of genome sequencing. Some people still are. They're afraid that if you get your genome sequenced you may learn things you're not really able to handle psychologically; that is, you may discover you're at risk for a disease that you can't cure and that would be devastating to a lot of people, and there was a lot of discussion when I first showed up at Stanford—this was in 2009—about whether genome sequencing can and should be used for normal healthy people because, again, they may learn devastating news that they're not prepared to handle. So, for a variety of reasons we thought it was just easiest to start with me, and it was really a proof of principle study. We sequenced my genome and then made various disease predictions, many of which actually correlated with my family history; things like higher incidence of coronary artery disease was one of the things that was predicted, we knew that from my family history, lower rates of obesity, we also knew that from my family history. But there were some surprises, and certainly the biggest surprise was this high risk for type 2 diabetes that popped up that I was not aware of from my family history, and that did show up early. At the same time we did these blood draws for sequencing my genome we actually decided to look at all the proteins we could out of my blood (meaning out of my blood cells; they are called peripheral blood monocyte cells), also out of my plasma and serum. So we were profiling proteins, metabolites, and RNA out of the peripheral blood monocyte cells, and we also looked at my antibody profiles because they are a pretty good marker for certain kinds of human disease, and we actually profiled my reactivity to 9000 human proteins and we also profiled viruses. And most recently; we've added on DNA methylation patterns, which lets us follow epigenetic changes, and we also profile my microbiome, meaning my stool, urine, skin, nasal, and tongue microbiomes, so five different microbiomes we're now profiling. The idea is to collect all this information and actually see how it changes across time when I'm healthy and times when I have infections. We've now been doing this for almost three and a half years, and we draw samples quite frequently when I have a respiratory virus infection. Believe it or not, I've also had six of those over these three and a half years because I have two little kids and they seem to pass their germs onto me periodically. So I've had six viral infections, three rhinovirus infections, one respiratory syncytial virus infection, and two adenovirus infections during this time. What we do is we do dense sampling when I have these viral infections, meaning we take blood as soon as I start getting some symptoms of being sick, and then we take it the next day, and two days later, and so on. We do dense sampling over three weeks, and then we do it every two to three months when I'm healthy, so fairly infrequently when I'm healthy, but quite frequently when I'm sick. In total we've now collected over sixty samples from me across these three and a half years, and then we profile for all these different "oms" that I mentioned before: the transcriptome, the proteome, the autoantibodyome, and the metabolites, and we also profile some very specific proteins as well—cytokines, which are great markers of your immune response, and such. And then we try and follow how all my molecules changed. Initially, we were following about forty thousand molecules in my blood, and now we make literally billions of measurements with the DNA methylation and the microbiome. We're trying to see how these change

over time.
What we discovered was, first of all, that I was predicted to be at risk for diabetes, and much to my surprise, I guess scientifically it was quite interesting, personally it wasn't what I was expecting, I did in fact get diabetes during this time that we were profiling. It turns out, actually, it came up right after a very nasty viral infection—the respiratory syncytial virus is when my sugar shot through the roof. And we caught it because we were doing all these other profiles, all these other "oms," and we actually caught it fairly quickly, and it didn't just shoot up for a few days; it was actually up for several months and we were doing all these subsequent tests, like hemoglobin A1c, and sure enough my blood sugar was very, very much up there, to the point where I was classified as diabetic.

Once I saw this it took several months to see that it was there and it wasn't going away—it seemed reproducible—that I actually dramatically changed my diet, which was not a very good diet, I have to admit, in the first place. I used to eat lots of desserts, lots of sweets, because I didn't know I was at risk for diabetes, or at least I didn't have it running in my family. Once my sugar did shoot up high I cut out all that and I increased my exercise (increased my biking and started running), and it took about six months but gradually I could bring the sugar levels down to normal range.

When I was diabetic, my hemoglobin A1c was up at 6.7. Once I brought it down to normal it was below 5. It was all managed without drugs. It has generally stayed pretty low ever since. The thing that was quite interesting was that also by doing all these other "omes" (meaning the transcriptome and proteome), we could see at a level no one has ever seen before all the different pathways and things that were changing, both during the time I got diabetes and also during the various times I was getting these viral infections. And actually we've discovered some new patterns, even since that first paper was published. We've seen very interesting cytokine fluctuations that occur after getting certain of the viral infections. It's really quite fascinating.

The bottom line is we can see the physiological changes that are going on at a level no one has ever looked at before, and as one person liked to phrase it, it's like we're now getting an IMAX view, if you will, of a person's molecular state and, in a sense, their physiological and their health state, by following all these molecules, whereas before it would be something akin to looking at a very low resolution, maybe noisy radio, is how I would classify the way we look at things today. It's just very low level, very crude, compared to what we're capable of doing. This is the direction I'd like to see medicine go.

Right now, everything I've told you is very much a research project; that is, it's like we're making billions of these measurements. We don't know which ones are the most meaningful just yet, but by actually doing this on large numbers of people—we're now trying to study 50 pre-diabetics to see what molecular changes occur when they get diabetes and when they see other periods of stress, like viral infections or other things that might be going on in terms of lifestyle stresses. So we're actually trying to follow all this, and we'll see what kinds of molecular changes occur, and ultimately I think we'll see a new kind of blood test come out where instead of measuring just 15 things as is routinely done, we'll probably be measuring hopefully thousands of things. And the other thing, I would say, is we would measure them much more frequently than we currently do as well. I'm not sure about all the listeners out there, but as a healthy person I used to go to the doctor I'd say about every 2 to 3 years. If I had done that during the time I got diabetes, I probably wouldn't have discovered it for another 20 months, so I think we'll need much more frequent measurements. This will be a bit controversial, but I'd like to see them set up as home tests, where you can actually do self measurements, or you might mail off a little blood

spot and get back a detailed report. You'd get these measurements much more frequently, and then if you saw something that looked a bit aberrant you'd go in and get more detailed follow-up tests.

The bottom line is I think we'll be able to see human physiology at a much, much higher resolution than we're currently doing with these various 'omics technologies, and ultimately this should have the power of driving medicine, which is now very much symptom-based—as people get sick we treat that. We've got to get away from that to a much more preventative and early diagnostics phase where you could predict someone's disease, try and avoid it, or minimally catch disease early when you can do something about it, like in my case for diabetes. You catch it early and you can manage it. If you catch it late, for most diseases it is very hard to reverse course, but you can manage it somewhat. So that's my story and some of my thoughts, there. I don't know if you have some questions for me.

Examining Inflammatory Regulatory Pathways in Diabetes Pattern Recognition Work

JB: First of all, that's just a revolutionary story and it's so inspiring. It's like having a window into the future. It's one of those looking glass opportunities. You know, as I looked at your PNAS article recently on the systematic functional regulatory assessment, I recognized that you talk a little bit in that paper about the nuclear factor kappa beta binding regions enriched in disease-associated SNPs. I'm wondering, in your diabetes pattern recognition work with the 'omics, did you see a confluence between the inflammatory regulatory pathways and the insulin resistance and prediabetes?

MS: That's a great question. We definitely saw the inflammation pathways go up during the time I got infected, and it was after that was when a series of pathways also changed that were related to the glucose metabolism and insulin signaling pathways. So, they were phased a bit. We don't know whether there is a direct cause or not yet, but of course it's very attractive to think there is some linkage there, certainly between the viral infection and its associated inflammation response and the glucose dysregulation. We certainly like to think that's the case. I think this is where we need to study a lot more people to see how often this happens. One other comment I could make on this is that diabetes is a very heterogeneous disease. In fact, we like to think it is probably a hundred different diseases and not one simple disease. It may be that some people do get diabetes and it is linked through things like inflammation, and for other people it may be linked in other ways; it may come out in a different manifestation. The one thing they all have in common is high glucose, but there may be many ways to get there. So that remains to be seen and I think the 'omics technology will be very useful for dissecting that out to see how many different diseases are there, and that may actually affect the way in which we treat these diseases; we may treat them all a bit differently.

JB: I think you just crossed a really important bridge for us in the functional medicine community. You're probably not familiar with what our definition of functional medicine is about, but it is basically focusing on mechanisms that underlie disturbances in physiology that produce what we later call—for convenience of nomenclature—diseases. We think diseases are kind of the manifestations of resting grounds before we understand mechanisms. As you've talked about with diabetes, being multiple different conditions that arise with the same phenotypic outcome called hyperglycemia, you can use that same model across a range of other diseases from the autoimmune family or from the cardiovascular family. That you may have a pathophysiological determinant at the histology level that you call a disease, but the mechanism by which you got there could vary significantly from patient to patient. The future, we believe in functional medicine, is you treat the cause rather than the effect; you understand the origin of

the disturbance in the physiology and you find how to treat that rather than what we call “naming and blaming,” putting all your eggs in the basket of the disease. You’ve just spoken eloquently about the whole concept that we, in 1991, formed the Institute for Functional Medicine around.

MS: I would agree with everything you just said. I think this can be true of so many different complex diseases. Even cancer, you probably appreciate now, as being stratified by either the genetic underpinnings of the disease and that’s how it’s being treated, and as people look more and more at, for example, breast cancer, they see more and more different subcategories; same with colon cancer. I think this will be true of virtually every disease people look at. There will be different underpinnings, and I think that’s ultimately how it has to be addressed, so I agree 100 percent with you, Jeffrey.

JB: Thank you. Since 1991, the Institute for Functional Medicine, which provides approved CME courses for physicians has had about, I think, nearly one hundred thousand physicians have gone through its courses worldwide since 1991. We’ve published a medical textbook in 2005 that was revised in 2010. The concept, then, led us to believe that this is a systems biology operating system for medicine. It’s still in the early stages. It’s a little bit like what Leroy Hood has been talking about with P4 medicine, trying to find a clinical algorithm that will be the top of the funnel into which we pour all this extraordinary information that we’re developing that you’ve described to help the clinician be more precise in how they’re going to manage that patient and their problems and hopefully get to a quantified prevention—a personalized prevention—which then leads me, lastly, to where that has taken us. We recognize that there was probably a rallying round of many different viewpoints and language systems and pedigrees and backgrounds, which is this concept that we call personalized lifestyle medicine. Everyone has a lifestyle, and we know that it’s a wildcard—it’s a variable—that modulates or modifies whatever therapy a patient may be put on. It can affect cytochrome P450 activities and drug detoxification. It can affect immune function…well, it can affect all functions of the body. We said, this seems to be the outlier in medicine because we often think of lifestyle as being soft and all this other being hard science, but yet when we really bring genomics into it, lifestyle—the gene-environment interaction—may become one of the most important modifiers of the phenotype over decades of living, particularly now that we get into understanding more about epigenetics. So we formed the Personalized Lifestyle Medicine Institute in January of this year (of 2013) to try to raise the bar and encourage discussion so that members of this community with divergent backgrounds and expertise might find this a common place for a quantifiable approach towards prevention and early disease management by looking at lifestyle through the same lens that we look at disease. We’re up now with a website. It’s quite remarkable, actually, the kind of response we’re getting. I didn’t realize it until we published an article in the medical press here two months ago that we were the first people to use the term, at least according to PubMed in this personalized lifestyle medicine concept as a word, or as a theme.[3] But it seems to me it ties together many of the things that we’re discussing. It’s early in its infancy, but it may be a place that is a meeting ground for people like yourself and others with different disciplines to really discuss how this gene-environment interaction really influences health and disease patterns.

Lifestyle is Multivariable and Hard to Quantify

MS: Sure. I mean, I agree again a lot with what you just said. I think one reason it is avoided is the lifestyle part. It’s the hardest thing to quantify, and it is so multivariable—there are so many different variables—that people often don’t know where to start. I think people are digging into this now. You’ve seen the simple devices people wear to measure all the steps they take, the Jawbone and the Fitbit and

other things that you can put in as apps on your iPhone, so people are starting to quantify other sorts of parameters. There's a long ways to go; measuring your food intake and all the various things that do basically integrate into lifestyle. I think there's a lot to be done here, and I agree with you that it is completely in its infancy. I think the other comment I would make and I think you alluded to, but to be more explicit, is I think things like the DNA methylation and transcriptomics that gives you information, we think, about your epigenomic state, and it's an indirect measure of some of these lifestyle impacts, I would say. So we're hopeful that some of these other 'omics will be a bit of a readout; an indirect readout of some of the lifestyle things that are occurring, that they will help us be more predictive about what sorts of possibilities might be happening with regards to your health. That is, if you get a viral infection does it leave a permanent mark or a semi-permanent mark on your DNA methylation pattern, which in turn could lead to acquisition of a disease, like diabetes or what have you.

We do want to get more 'omics measurements to get these readouts, and I think also quantifying more of the things that you just talked about—the various toxins that people get exposed to in the food they eat, all the sorts of things I think will ultimately be very, very powerful not only in understanding human physiology, but being able to make predictions. Ultimately, it comes back to that Gattaca movie; we want to be very predictive about both the combination of our genetics and our environmental lifestyles that will make things very predictive about possible outcomes, and that way we'll be able to manage health care much, much better.

JB: I can't tell you how much I appreciate both your insight and time. I would call this discussion, for me, comparable to two other epic discussions I've had the privilege of having on Functional Medicine Update, one was with Moshe Szyf at McGill University, who is in the labs of Hans Selye. He and his coworkers have been looking at epigenetic imprinting by psychobehavioral changes in the animals' environment. You might be familiar with some of this work—how they show that methylation patterns change with nurturing and with stress patterns in the animals' environment that then alter expression patterns of cassettes of genes that are associated with alarm genes. So they talk about things like posttraumatic stress syndrome and how they get locked in by epigenetic programming, basically. And then I also had the privilege of interviewing on a couple of occasions Randy Jirtle at Duke, who has done some really wonderful work on nutritional epigenomics. I think you're probably familiar with his work with Bob Waterland where they looked at the methylating nutrients—folate, B12, and B6—in pregnant animals (in the Agouti mouse, actually), and showed how they could modify the fur coat and form these pseudo-Agoutis that don't get fat, and they don't get diabetes, which are conditions that their parents with the same genes, are predisposed to getting.[4]

I think there is a tremendous frontier that is opening up thanks to work of people like yourself to really change the complexion of medicine from being a deterministic medicine to being a very modifiable form of health care. If you know the answers to the right questions you can get entirely different answers.

MS: I agree. It all sounds great.

JB: Thank you very, very much. We're going to follow your work very closely, and I can't tell you once again how much we appreciate your sharing what you've done.

MS: Sure, thanks again for having me

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