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The Future of Genomic Medicine (FGM) III

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From Medscape Medical News

The Genetics of Infectious Disease: An Expert Interview With Nicholas J. Schork, PhD

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March 24, 2010 — *Editor's note: Genomic research into infectious disease susceptibility is especially complex because at least 2 genomes must be taken into consideration — that of the host and that of the microorganism. Infections from methicillin-resistant* Staphylococcus aureus *(MRSA) and other pathogens primarily reflect the genomics of the agent; on the more positive side, studies of the human microbiome suggest a delicate, often beneficial, balance between microorganisms and the human bodies they inhabit.*

In an interview with Medscape Pathology*, Nicholas J. Schork, PhD, moderator of the session on the genomics of infectious disease, and director of research, Scripps Genomic Medicine, at Scripps Translational Science Institute in La Jolla, California, discusses recent advances in the understanding of the genetics of hosts and pathogens in infectious disease, as presented at The Future of Genomic Medicine (FGM) III, held March 5 and 6 in San Diego, California, and cosponsored by Scripps and the J. Craig Venter Institute.*

Medscape: What do you think the topics selected for this year's conference show about the way genomics research is developing?

Dr. Schork: The first year of the conference [2007] was more about technologies — people's thoughts and visions about how to leverage some of these technologies to do things. But in as little as 2 years, people have started to apply these technologies in ways that could impact clinical practice, and studies are starting to be pursued.

There are a couple of good examples. Three years ago, you had 1 whole-genome sequence, and that was Craig Venter's. Now we're up to something like 17, and the number is growing, and that doesn't reflect all the unpublished sequences that people are still working on. So there are some dramatic improvements in the application of sequencing technologies to our understanding of the human genome.

Medscape: The first whole-genome sequences were sort of proof of principle, but what is being found out from the ones that are being done now?

Dr. Schork: Now with whole-genome sequencing, you can sequence the heritable genome — your germ-line genome — and compare it with what is in your somatic cells, like cancer cells. Elaine Mardis [PhD, Washington University, St. Louis, Missouri], for example, described studies she's involved in where she has taken people's tumors, sequenced the genomes in those tumors in their entirety, and then sequenced their germ-line DNA. She could then identify variations that were not inherited but were present in the cancer, and those mutations must have arisen during somatic cell replication and contributed to tumorigenesis. That is an amazing kind of thing, and now it's a reality.

Medscape: You chaired a session on infectious disease. Is that your personal research area?

Dr. Schork: I actually do a little bit of everything. I'm a human geneticist, and this is one area of interest of mine — understanding how pathogens do what they do to our human host. So, yes, I've had that project brewing for some time, and it was good to actually present something on it.

Medscape: Can you give a capsule summary of what you talked about in your presentation on MRSA?

Dr. Schork: What we did was sequence different strains of MRSA. We had some strains that caused an invasive infection — a pathogen that kind of bored through the skin, right down to the bone, and started eating away at these people. Invasive MRSA of this type is a true public health disaster. It's been discussed by the [Centers for Disease Control and Prevention] and in editorials in the *New England Journal of Medicine*, because no one quite knows how to deal with it. Then, there are noninvasive forms of MRSA that, if you're

infected, will give you a bad rash. The way to treat it is to literally cut out or cut off the skin harboring the infection, and then you can be sent on your merry way. It's painful, but it's more or less an outpatient treatment.

With invasive MRSA, you're in the hospital, you're in the [intensive care unit], you're going to die if they can't figure out how to stop it — it's really bad. The issues now are that there are a few genetic markers that people have identified that can distinguish the more benign form from the more invasive form. So what we did was sequence a bunch of invasive forms and noninvasive forms — forms in which an individual actually died and forms in which the individuals infected by them could be treated and sent home.

We're starting to identify markers that might distinguish the 2 strains and can give us insight into how to develop a panel of markers that can distinguish the strains, should somebody walk in and present signs of MRSA infection, and also to identify fundamental pathways or genetic mechanisms that contribute to the invasive nature of the more deleterious strain.

We also found — or have some evidence anyway, and we're trying to validate this — that the noninvasive strains tend to be developing greater genetic diversity over time than the invasive strains. Why would that be going on? One answer that we find very interesting, but again we need to validate, is that maybe the less invasive strains are evolving away from the more invasive strains. In order to survive, they don't want this property of being very deleterious. The reason for that is — and this is known among people that study infectious disease — a pathogen cannot propagate if it kills its host quickly, because it just dies along with the host. There's got to be some balance between the infection's ability to thrive off the host and keeping the host alive long enough to contribute to the propagation of the pathogen to another host. We think this greater diversity might reflect the fact that the noninvasive forms develop mutations and genetic variations that are selected for on the basis of their *noninvasive* nature.

Medscape: You described the invasive forms literally boring their way through the skin. Are there other organisms, maybe not antibiotic resistant, that have the capacity to bore their way into the body — without such deleterious effects?

Dr. Schork: There are forms of Staph that aren't resistant to methicillin, that can be killed by methicillin. Those are known as methicillin-sensitive *S aureus* strains. If you were to let those strains grow unchecked and *not* kill them with methicillin, they would wreak damage. There are strains of Staph that could be just as invasive as MRSA, but you can control them with drugs.

The problem with invasive MRSA is that it's eating up its hosts, and you can't combat that activity with standard drugs. The last slide in my presentation mentioned a very recent editorial [February 27, 2010] in *The New York Times* by Andrew Pollack [entitled Rising Threat of Infections Unfazed by Antibiotics], in which he talked about the rising threat of bacterial pathogens. He mentioned MRSA, along with some Gram-negative bacterial pathogens (MRSA is Gram-positive). It turns out that these bacterial pathogens are true public health nightmares. What he suggested was that there was little investment in the pharmaceutical industry to develop drugs to combat these sorts of bacterial pathogens. And yet, all things considered, they might be the most deadly of things that could contribute to very, very sad public health outcomes.

Medscape: Maybe we could move to a more cheerful topic! Could you talk about the research that's being done on the microbiome?

Dr. Schork: The microbiome is the totality of all the organisms that tend to populate the human body, and the numbers are staggering! You have millions of little species, organisms that populate your body. That includes in your gut, on your skin, in your mouth. What we can do with DNA sequencing is take samples of the species that populate these various parts of the human body, sequence the DNA from these samples, and get an idea of how many different species are in any of these sort of ecological niches in the human body and what properties those different species have. [We can determine whether] they participate in processes like the breakdown of some particular material in those body cavities, [whether] they [are] deleterious in nature, [whether] they do more harm than good, and what those organisms might be about or do. It's really a way of surveying what populates the human body. Those studies are being pursued more and more often and with greater sophistication.

Medscape: How much is the microbiome influenced by the genetics of the host? If someone tends to have oily skin or a more acidic gastrointestinal tract, would that change what microbes inhabit their body?

Dr. Schork: It absolutely does. There was a paper just published in *Nature* (2010;464:59-65) in which the researchers studied the human gut microbiome and showed that the microbiomes of people with and without inflammatory bowel disease were different — suggesting *either* that the treatment for this disease influences one's microbiome, *or* that the fundamental pathologies associated with this disease contribute to a different habitat for the species that might collect there, contributing to these differences. What some of these people studying the microbiome are trying to do is find out what species are really complementary to the human body, in that, without their populating the human body an individual might be less healthy.

You can imagine that there are certain processes that go on during digestion; some of these organisms contribute in a beneficial way. If you didn't have them, maybe you wouldn't be able to digest food as easily or in the same manner. So if, in fact, you can find someone who has digestive problems who *doesn't* have these little organisms in their microbiome, then one treatment might be to give them some of these organisms.

If you go to the health food stores — and some of this you have to take with a major grain of salt — you'll see these probiotic drinks and other things that contain healthy microorganisms, such as yogurt laced with all this stuff. Not that those things are currently based on science, but you can imagine at some point in the future, as we gain more insight into what species are beneficial, you could create such drinks with the appropriate microorganisms.

Medscape: Haven't we caused some of those problems in the past by taking antibiotics, which upset digestion for a week or so?

Dr. Schork: Absolutely. There are treatments . . . that try to clear out everything in your colon. That might be doing more harm than good because there are some species that are likely to be beneficial for certain processes.

You have to keep in mind that the human body has been around for a long time. There's been coevolution between the host and all these microorganisms, and they've probably found a very delicate balance, where each contributes to the benefit of the other. If you were to take away some of these more beneficial species, that could do more harm than good. The body has evolved to accept them and work with them in some way, so there's sort of a symbiosis there.

Medscape: Were there any controversial discussions at the conference, anything that people were at loggerheads about?

Dr. Schork: I don't know if this was a controversy — more of an interest on the part of attendees who wondered to what degree genomics could be brought to bear on understanding pathogens to the point where we could do something about them. If a news reporter like Andrew Pollack is painting this somewhat apocalyptic view of the potential of bacterial pathogens, how can we combat them? If we can leverage genetics and genomics to identify new drug targets or understand their evolution, then we may be able to head this disaster off at the pass.

There weren't many controversies [here at FGM III], but there was a patent curiosity in the audience. For example, Michael Hayden [MD, PhD], from the University of British Columbia in Vancouver, described a critical trial actually testing the utility of genetic testing in clinical contexts. This is clearly a research area in which the field is going to have to go. It's one thing to say, "Look, I found a genetic variation that's associated with drug response to HIV treatment" or, "I found a gene that's predictive of type 2 diabetes" — all the papers that are published and many of the speakers at the symposium described such studies. But if, in fact, you really want to change the face of clinical practice, you're going to have to show that using this information leads to better clinical care. And by "better", I mean both saving lives and not costing people zillions of dollars.

Michael Hayden described 2 clinical trials that are asking [whether], if one were to use genotyping to lump people into categories — you should get this drug, you should not get this drug; you should be on this regimen, you should not be on it — it actually makes a difference. It's one of the few research groups in the world that is engaging in a full-blown, randomized clinical trial [RCT] to evaluate the utility of genetic and genomic information in clinical settings. This might show how quickly things have evolved because, again, 2 or 3 years ago, people were thinking "we have to discover such associations," or "we have to develop better technologies to identify genetic factors that might influence drug response or diabetes susceptibility," or whatever. Now, 3 years later, we have at least one group, and I'm sure there are others actually testing, in an RCT-like framework, the utility of all these insights.

Medscape: Is there anything else you'd like to comment on, anything you'd like to get out there to clinicians?

Dr. Schork: One thing that was mentioned at the conference by Eric Topol [MD, director of the Scripps Translational Science Institute and chief academic officer for Scripps Health] is this new Association of Genomic Medicine, which is about credentialing and other sorts of things to enrich the clinical community with insights and resources. If physicians don't want to buy into genomic medicine, they're going to be swept over with this massive tidal wave of findings and clinically relevant insights. It really behooves the clinical community to pay attention to this stuff.

Time and time again, people in the audience asked: "What if I were to take my genetic information to my local physician?" You can get genetic risk assessments through Navigenics and 23andMe, and you can be genotyped. There are all sorts of things consumers can do that have a bearing on their health status or disease risks, that leverage genetic information. Obviously, if you wanted to walk into your physician's office for your check-up and hand your physician that information, the physician should be prepared to do something about it,

or at least talk intelligently about what it means. I don't know if there's been enough sensitivity to the need to educate physicians about what's about to occur — this big tidal wave.

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