Future Directions in Clinical Diagnostic Standards Development
Michael Amos, Ph.D.

DR. TEUTSCH: Our final speaker is Mike Amos, who we all know. He will talk a little bit about the future directions in clinical diagnostic standards development.

Mike, we are going to hold you to your 10 minutes so we do have time for some discussion at the end. Take it away.

DR. AMOS: Not a problem, not a problem. Thanks for your attention. I hope you appreciate the level of detail and precision that my NIST colleagues go to to provide standards for the various applications. I think John's table that talked about the various levels of who uses them and then Dave's table talking about the horizontal versus vertical standards gave you an idea about how we think about things.

I should probably bring my other hat up here because my boss, who is Dr. May, told me to put this disclaimer on here. I'm going to talk about things that we have learned over the last couple of years through many talks with many different people about what they consider the future of diagnostics and where things are going. At the same time, these are not official NIST programs or ideas but just food for thought for you.

What I want to talk about today are some of the harsh realities that are really going to drive health care change in the future, some lessons learned and what I think will happen, the fact that laboratory medicine will drive a lot of this change, some measurement challenges and the role measurement technologies and standards will play, and a potential plan to enable the change.

Where we are is kind of scary when you consider that about 83 percent of our total health care costs go to cover chronic diseases, whereas the rest of it is only about 17 percent. This constitutes almost $1.7 trillion out of the $2 trillion that we spent in 2005. Forty-three percent of that is spent on hospitalizations. The scary part is the most expensive to treat are among the fastest-growing reasons for hospitalizations, according to AHRQ.

Millions of people suffer from diseases that there is little known about the genetic basis. We have a growing number of problems with kids taking drugs for chronic diseases. More and more kids are being diagnosed with chronic diseases for which they are being treated. Diabetes is running rampant and growing at a rate of about, I think, 5 percent a year for type 1 diabetes. Kids under the age of five are now taking drugs for type 2 diabetes.

The problem is that things are not going that well in medical research. The innovation gap is really widening. There is more money going into research with not great returns on investment. There are more and more manufacturer-reported adverse events to the FDA all the time. It has grown dramatically since 1990, with billions of dollars of drugs coming off the market because of toxicity.

The future is not that great for diagnostics, really, if you base it on what has happened since 1995. This is, as best as we can tell -- and Steve's group helped me put this together -- the complete list of single protein biomarkers that have been approved by the FDA. There may be one or two recent ones. But I went through the FDA website again before I did this, and I couldn't find any more.

So things are not really looking that great in the future. Our grandchildren are going to be spending more money than they earn on health care. Like Steve said, these trends are not sustainable and a new development paradigm is really needed.

So, what have we learned. We have learned that the human body is very complex. It is really not just made up of all those individual components. Really, disease is caused by perturbations in very, very complex biological networks. It is not simple pathways anymore. Forget what you learned in high school. There is no such thing as a metabolic pathway. It is one of these globby things.

So, what have we learned. Disease is a result of perturbations in these pathways. Genomics has been helpful, and it will continue to be helpful but it is limited. Only a very small number of single protein biomarkers are good indicators or predictors of a limited number of diseases, and more complete understanding of human physiology is needed in order to identify good biomarkers.

What is going to happen. Medicine will focus on keeping people well. It has to. The only way we are going to really catch up in health care is by keeping people out of the hospital. That is possible. The way to do it is the fact that laboratory medicine will probably lead the way. -Omics will dominate. Complex disease signatures that are comprised of hundreds or thousands of data points will really be the biomarkers of the future.

Drug companies will develop their markets around interventional therapeutics and treatments like cholesterol and statins. They will use the same model. It will be based around these complex disease signatures. Disease signatures are measurable alterations in complex biochemical networks.

So, what happens. You get abnormalities in all this stuff, and you can do multiplex measurements and computer integration to develop disease signatures. There are a bunch of these things. We have no idea what these disease signatures are going to look like. Probably, it is going to be some sort of risk score, a number from one to 100, whether somebody is going to get this disease or not, but we really don't know what that is going to be. We hope that it is going to enable scientists and physicians to make better decisions.

Discovery decisions will increase the drug pipeline and all those things. Better clinical decisions help people, not just the drug and diagnostic companies.

Really, in between wellness and symptoms are these transitional states. That is where the focus is going to have to be. We are really looking at markers that occur years before disease symptoms occur. They often occur long before people realize they are sick.

They are unique biochemical markers. They can distinguish health from sickness. They are going to be person-specific. The rules of clinical trials are going to have to change because each person will end up serving as their own control.

There are typically going to be parameters in blood. Those probably are the true biomarkers that we are all looking for and that could be detected with proper technology.

A disease signature is like a radar signature. A good radar operator can identify a blip on a radar screen that is a bad guy versus a good guy. What we want to be able to do is develop similar technologies in the future for diagnostics.

One potential concept is being espoused by Dr. Lee Hood, who talks about organ-specific blood protein fingerprints as a potential way to do this. He calls it systems medicine. It integrates measurements and computers. It is basically taking a drop of blood, putting it on some analytical platform, putting it in an instrument, and then getting some data out to enable the complete visualization of what is going on in your body. That is the dream.

Why is this critical and what is going to happen. Today the healthcare markets are based on the number of sick people. Every drug company bases their market numbers and projections on the number of people they can treat. That is based on the number of people that they project will come down with a disease based on historical data.

The metrics of morbidity and mortality show the outcome is that people suffer and die of chronic diseases. It is not changing. We will see $4 trillion in healthcare costs projected by the year 2015. Like Janet Woodcock said, that is probably not sustainable.

The healthcare markets could be based on the number of people with preventable diseases. If that were the case, the metric would be the number of people positive for a valid predictive biomarker. The outcome would be that more people would die of trauma and in their sleep from old age, rather than spend 70 percent of healthcare dollars in the last two years of their life in terminal care.

Potential savings are, just for diabetes, probably at least $50 billion. Diabetes is more expensive to treat than cancer. We all know that.

What is going to happen is visualization of disease signatures. What kind of standards will be needed for this type of thing. We are really talking about the complete spectrum, but we will have to take a very logical and structured approach to it and take into account all the things you heard today from my colleagues: horizontal versus vertical standards, and what are the highest priorities of things that we should go after.

That is really what Willie talked about. We felt, and the community felt, that protein measurement science is probably one of the biggest challenges.

These are some of the things that we are going to have to do. But two fronts are really to promote discovery of disease signatures and then, on the back end, clinical analysis of these disease signatures.

I love my boss, but I have to disagree with you. We will always have this conversation, Willie. I think, coming from industry, if I had had a set of standards that I could anchor my tests against where I didn't have to guess and empirically try to figure out what my assays were really doing, then I could have sped up things a lot in my assay development.

I think the things that Dave is trying to do with proteomics and anchoring what I call the platform standards of mass spec to make sure that your mass spec works properly, are going to really drive the future.

You have transition states and systems medicine. That is one approach. Developing disease signatures to usher in the age of individual therapeutics and improve quality of life and help in economic security, which is, as Willie showed, part of our mission.

What is preventing us from getting there. Basically, it is the capabilities of doing these things, among many other things, but these are pretty much the major issues. It is really doing these types of measurements and the ability to analyze these types of things.

Here is a potential opportunity and a potential way of stimulating the advent of new technology. I think we are woefully deficient in our ability to measure proteins, and that is a real issue. I think we are at about the same place we were at the beginning of the Human Genome Project.

One way to stimulate interest is to have a mission to the Moon. So here is an idea. Maybe we can put a stake in the ground and say we can identify disease signatures for the most important diseases by the year 2020. The number is obviously subject to debate, but these are the kinds of things that we would have to do and hopefully will enable some new approaches and a better way of looking at diseases and keeping people healthy.

What do we hope to learn? We have some pretty lofty goals here, but I think without new technology it is not going to happen.

One thing I can say is, when I came to NIST I was pretty ignorant of all this. I hope that the presentations today really helped you get an appreciation for what my colleagues do. I am amongst egghead scientists who focus on the nitty-gritty, nuts and bolts of measurement, and I think that that is why we are here. I appreciate your attention.

DR. TEUTSCH: Thanks, Mike.