

**Metabolomic Tests**  
***Karen Phinney, Ph.D.***

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DR. TEUTSCH: Now, metabolomics. Dr. Phinney, welcome.

DR. PHINNEY: Thank you. I'm very happy to be here today. I appreciate the invitation. For those of you who are unfamiliar with metabolomics, this is something that has been going on in clinical chemistry for a long time. We have been measuring small molecules like glucose and cholesterol as part of diagnosing disease. To a great extent, this is just a fancy name for something that has been going on for a long time.

Metabolomics really represents the endpoint of genomics and proteomics. It is what you really get when you look at a sample of serum, plasma, or urine. Those samples reflect the exact processes going on at that period of time.

There are some advantages to looking at the metabolome. It does represent an exact picture of the situation in the body at that point in time, and it is affected by things like diet, stress, exercise, disease, health, you name it. So instead of looking at the genome, where you look at what might happen, you actually look at the phenotype or what really did happen. To a great extent, this could be the ultimate in really doing disease diagnosis.

There are some other things to know about the metabolome. It is simpler than looking at either the genome or proteome. Even though in the metabolome you are still talking about thousands of potential metabolites, that is still a far simpler situation than thinking of hundreds of thousands of different proteins or even tens of thousands of different genes.

So, what is the goal of metabolomics. Why are we throwing around this fancy terminology. As I mentioned, we have been using metabolites as diagnostic markers for a long time, but we have tended to do them one at a time. We might look at glucose to diagnose diabetes and we look at cholesterol to look at risk of heart disease. But we haven't put all those pieces together. So what is unique about metabolomics is that it involves looking at panels or signatures of different analytes and their levels under different circumstances in the case of health or disease.

Ideally, you can use those patterns or those signatures to try and segment people into different groups and, ideally, use that as a way of doing disease diagnosis.

If you look at the picture that is there on the left, that is an NMR pattern or NMR analysis of a particular sample. You can see there are lots of different peaks there. You can see, looking at the different color of spectra, that there are some differences in how those appear.

The goal of metabolomics is to try to look at those different patterns and to be able to say something about different levels of particular metabolites representing some signature. So, does it represent a healthy person or a diseased person.

Ideally, we would like to get to the situation that you see on the right, where you can put people in different boxes and say in this particular population we see this signature or these different metabolites at these particular levels and in a healthy person we see a different pattern. If you can do that with some reliability, you could use that as a diagnostic tool.

Now, one of the reasons to do this is also to try and identify places where we could intervene in a disease state. If we know that in a particular disease certain metabolites were elevated or

decreased, we could then try to intervene in that particular metabolic pathway through pharmaceuticals or some other therapy. So metabolomics does represent one potential mechanism to identify new therapies, and there is certainly a lot of activity in this area in the pharmaceutical industry.

The drug industry is also interested in looking at this as a mechanism to identify toxicity. If you can identify particular markers that indicate liver toxicity, for example, and you can measure those in a multiplexed way, you might be able to predict ahead of time whether a particular pharmaceutical is going to have adverse effects.

That would certainly be very valuable. We know these days we hear a lot in the news about things that make it onto the market only to be withdrawn later. Certainly, that is why the pharmaceutical industry has such an interest in this area.

Finally, as you saw in one of the first slides there, all these things are related. The metabolome can be traced all the way back to the genome. If you look at patterns of metabolites, you might be able to say something about gene function that assumes something about the metabolome, the proteome, and the genome all at the same time. That is quite a lot of information to try to capture, but under ideal circumstances you might be able to do that.

So, what are some of the issues. Where does standardization come in. If you think about trying to measure thousands of metabolites simultaneously, you are talking about very large and complex data sets. As David mentioned, there are always issues in terms of instrumentation, sample collection, and sample handling. So, how can you get to a point where you can say with some certainty that the pattern of metabolites that you see is really representative of a particular condition.

There are a number of these issues: sampling, instrument variations, platform variations, and software, just in dealing with these very large data sets.

Once you get your data, how do you pick out which things actually mean something. There are thousands of metabolites but maybe only three are relevant to the particular condition that you are studying. This comes down to software and it comes down to making assumptions about the data that you have. Clearly, in those situations there is room for error and there is room for differences in interpretation.

Finally, before we can get to a clinical diagnostic setting, we need to actually validate that the patterns of metabolites we think are useful in diagnosis really are. Certainly, that comes back to looking at large populations of people and making sure that you really can say with some certainty that you are making an accurate diagnosis based on this metabolite signature.

About two years ago, I guess, NIH came to us. They have been funding a number of investigators for metabolomics technology development. But along with that effort they realized the importance of some standardization and some common way for people to evaluate the technology that they were developing, some common mechanism for them to use. So they approached NIST about developing reference material for metabolomics.

We have been involved in that effort over about the past two years, and this material will be introduced I think probably early in 2009. So we are coming close to at least the end of the first stage of this process.

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This reference material is actually a plasma pool. The reason that we did that is we didn't want to represent any particular part of a population. We wanted this to be indicative of a mix of male and female, different age groups, and healthy individuals, and we wanted it to also have some of the ethnic characteristics of the U.S. population. So the samples that were pooled to prepared this material came from African Americans, Asians, Caucasians, and, again, both male and female individuals.

One of the reasons that we did that was that when we have to prepare this material again in, say, 10 years, we wanted to be able to prepare it in a very similar way. That is why we set these criteria in designing the material.

We have a lot of experience in measuring individual metabolites. As Dr. May mentioned, we have a number of different reference materials for individual metabolites in serum, the traditional analytes like cholesterol, glucose, and creatinine. We have measured those same analytes in this particular reference material, so we will have certified values for probably 40 different metabolites, everything from fatty acids to glucose, to hormones.

But we also realized that people want something more than that. They would like to know what other metabolites are present. So the effort that we are focusing on right now is more of a qualitative effort to see what techniques do we have available, either at NIST or through collaborators, where we can identify additional metabolites and also provide that information.

Clearly, there is the potential to use this material in a variety of different ways. Depending upon your particular study, if you are looking at glucose metabolism or if you are looking at kidney disease, your interests may be different. So in order to make this material relevant to as many different people as possible, we are trying to provide as much information as we can.

Now, clearly, this is a starting point in terms of providing standards for this particular area. It is an evolving field, and we certainly recognize that. We do see the potential for additional reference materials and different standards here, and also tools in the area of bioinformatics. One of the big questions here is how do you handle these large data sets. How do you insure their reliability. How do you compare data from different instrument platforms or different laboratories. I think these are all questions that will be coming up as this field moves forward. It is still very early on.

We also realize that there may be a need for reference materials to focus on more specific populations. It might be a group of individuals with heart disease or it might be male versus female. The list could go on and on. Certainly, we look to the field to help us in prioritizing those efforts.

There are some fledgling standardization efforts in this field, particularly in the area of data reporting. So we are also working with those organizations to offer our insight into metrology and to learn from them in the areas where NIST can contribute in terms of standardization.

With that, I will close. I know we are going to have time for some discussion here at the end. I appreciate your time.

DR. TEUTSCH: Great. Thank you very much. I think what we will do is continue on. Then we can take questions at the very end.