

**Clinical Perspective**  
*Jeff Cossman, M.D.*

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DR. TEUTSCH: That last slide is going to give us a lot to think about.

I'm not sure where to go. I guess we will go to Dr. Cossman.

DR. COSSMAN: That is a tough act to follow.

DR. TEUTSCH: Thank you for being here and talking about a little bit about the clinical perspective from the Critical Path Institute.

DR. COSSMAN: Thank you very much. Steve Gutman is a tough act to follow. But, Steve, I just want to say thank you for all your service at FDA. It has been a real pleasure working with you, and I look forward to whatever you are doing in the future and maybe having a chance to work with you that way, too.

I'm here to talk to you today about something that we are doing at the Critical Path Institute which may impact standardization of diagnostics in genetics. Let me explain as we go along here what this concept is.

In the development of diagnostics, we can expect delays not just because FDA regulates it but delays in many of the regulatory paths of diagnostics. Many times we see surprises. A diagnostic manufacturer may submit an application to FDA and it may be returned saying, you need to do this again, the data is not prepared in a way that we need, we don't understand it, and you need to redo this for a variety of reasons.

Or there may be surprises on the part of FDA, receiving data that they say is inconsistent or shoddy or not the way that they needed it in the first place.

In order to reduce surprises from either side, we have started to create a standards method that might help both the diagnostic manufacturers and the FDA communicate with each other.

What is needed for this change. This is something that has been a pattern that we have used through Critical Path Institute. We are a nonprofit agency that is not part of the FDA, not part of industry, and in fact is not part of the government at all. It is a neutral party that helps in communication between the FDA, industry, patient advocacy groups, and researchers in order to communicate among them around science; to improve the methods that are used to develop drugs and diagnostics and bring them to the public and to the consumers.

We have a number of consortia at the Critical Path Institute, or C-Path, which involve multiple companies signing agreements and working with FDA, and in some cases EMEA in Europe, to create best-of-class methods. These can be in safety; efficacy; in the case of Warfarin, dosing; and in the case of Alzheimer's disease and Parkinson's disease, a coalition against major disease in which the largest pharmaceutical companies in the world sign an agreement to work and share data.

What we are talking about here in all of these cases is a way of verifying the quality and accuracy of biomarkers; sharing information across these groups; finding out what is the best-of-class method for predicting safety or efficacy in a particular condition and sharing that information; agreeing on a consensus on what is the best-of-class method; and having FDA accept this method

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so that when a company comes with a new submission they will know that the FDA already understands these biomarkers and has, in a sense, preaccepted them as part of their application for a new drug.

Now, what we have seen in running these consortia, because C-Path creates and leads these consortia, is a common theme of diagnostics that are needed. What we felt was there may be a role here for establishing an entity that could provide a means for standardizing the testing of diagnostics before they are submitted to the FDA.

We see many bottlenecks along the way. There are problems in the development of the data that goes to the FDA and the creation, as you have heard, of standard samples. Ten companies may have an assay against, say, troponin or d-dimers, but they are not testing them against the same standard analyte sample. So the data that is coming in to FDA may not necessarily be comparable. So if you are looking for a me-too device or a 510(k), we can't always prove that the test is equivalent because it hasn't been tested on the same clinical material.

What we are trying to do is reduce the number of surprises that FDA is giving to industry, telling them to redo the study, or the other way around, surprises to FDA from industry. We want to look at ways to improve the efficiency of the requirement for the highest standard of approval at FDA, which is the PMA, and how companies can improve their efficiency in getting to that very high bar.

Finally, there are bottlenecks, as you have just heard, in lack of evidence for payers. How does a payer know whether the test performs as required. An insurance company or CMS is going to pay for a test. What evidence does it have that that test is valuable and actually does the performance that it claims that it does.

So, how do we improve. We improve by the ways that we have already done in the other consortia that we are involved in, and that is to find the best-of-class methods, to look for real proof and real evidence of reliability, and also for a standard submission process. In other words, multiple companies submitting data now submit them in different formats, different kinds of data, different ways of analyzing the data, different clinical samples. Why don't we standardize that and make life easier for those reviewers at FDA who are looking at diagnostic device applications.

So what we thought was, what we don't have for diagnostics is an underwriter's lab. This would be not a proficiency testing agency like CAP but, instead, further upstream in the pipeline. Diagnostic manufacturers develop tests, submit those for beta testing, say at universities, and that data goes into the submission to FDA.

Why not have a standardized format, a single agency whose sole focus is only on evaluating these diagnostic tests before they are submitted to FDA. They can be an independent body and put a seal of approval on it saying, yes, this test did perform as claimed. We ran it exactly the way it says in the manufacturer's instructions. We ran it on standardized samples. We can attest that, with no incentive as to whether this test is approved or not, it did perform as claimed.

Why not do this in diagnostics. It is done in many other industries: in semiconductors, in food safety, for drugs. This is not a new idea. It is just a new idea for this particular industry.

To quote a famous poet, Steve Gutman, we see that the FDA is interested in this. You have just heard him say the FDA is interested in finding standards for diagnostics. In this case he is talking

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about targeted therapy. Our original plan was to focus specifically on targeted therapy in cancer, but for this standards laboratory we have heard from industry that they would like to see this service applied and be available for any kind of clinical laboratory diagnostic.

So what Steve told us, as you can see in the middle paragraph, this could be "a template for the validation of diagnostics in targeted cancer therapy," but any kind of therapy. This could be a template and a way to evaluate diagnostics before they go to FDA.

The concept here is to have two levels of evaluation of a diagnostic. One is simply performance. Does it tell you the correct level of whatever the analyte is.

Second would be a much more complex one, and that would be where you have outcomes information attached to the clinical samples so that you could determine the relative value of this diagnostic in predicting a clinical value such as response to therapy and association with a particular clinical condition.

That information would be put into a report, certified as to the accuracy of the test, and then that data could be used voluntarily by the manufacturer in their submission for FDA approval.

So, what needs does this type of testing meet. One of the goals here is something that this session is all about: having a standard repository of samples that could be used and normalized, and to create methods so that they could be reused as consumed. Then tests could be analyzed on the same samples repeatedly and competing tests could be compared if manufacturers wished to.

It would be a neutral site. It could determine whether or not a new test equals the predicate, or is equivalent to it. For lab-developed tests such as genetics, which may not end up being submitted to the FDA as an in vitro diagnostic, it could be used to evaluate those as well so that providers, consumers, payers, and investors would know whether or not the genetic test or other laboratory-developed test performed as claimed. In other words, did it detect the SNP. Did it do what it was said to do.

What does this do. It improves reporting to FDA, hopefully improving for the diagnostic manufacturer their chances of having their data accepted. Second, it does provide a format for comparing competing products. If companies wished to, they could have their assays run in a bake-off. You could have multiple companies competing with the same assay, all tested at a neutral site on the same analytes.

All of this information, whether it is competing or whether it is single case-by-case information, provides evidence to the community that needs to know whether or not a test performs as is claimed.

Now, we have talked about this. We are now starting to develop this laboratory. We have seed funding. It is starting in the State of Arizona. The state has provided an economic development package. We have a couple of people who are helping to start this here today with us: Mary Ellen Demars and Ralph Martel. We are looking to take on our first demonstration case, whether it is in genetics or in cancer. We are not sure yet. We are looking for ideas that would fit very specific criteria for first demonstration cases.

Because people have heard about this, we have been asked a number of questions. One, is this just another regulatory hurdle, which is exactly what I would think this is. I used to run a clinical laboratory. If I had heard about this and didn't quite understand it, I would think the last thing I

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need is somebody else coming into my laboratory to inspect it and regulate it and find something else wrong.

This is not what this is about. This is not a regulatory body. It has no regulatory authority. It is completely voluntary. The whole idea is to be helpful to the manufacturer or the developer of the diagnostic.

How does this United States Diagnostic Standards Lab, USDS, relate to federal agencies and other agencies that are involved. We are looking at ways of becoming synergistic and complementary. We have had detailed discussions with NIST and Mike Amos as to how they could develop standards for the platforms for this particular testing, as well as with many of the other agencies across federal government.

What happens if the test result comes out and it is not acceptable or not useful to the manufacturer? They don't have to use it. They own that data. It is their data. They can keep it. It is not published. They can do whatever they want with it. If they don't want to use it, they don't have to use it. They will pay for it. They will be running a fee for service and they can have the data, but if they don't want to use it, they don't have to.

How is IP protected? Everything that is run is confidential within this standards laboratory. If there is any kind of intellectual property or special methods that are being run, those will not be revealed unless the manufacturer wants it to.

How will reference standards be maintained? You have heard methods that are used for that. We know that we need to do that on a case-by-case basis as we enter into this space.

That is the story. I thank you very much for listening and for your attention. Thank you.

DR. TEUTSCH: Great. Thank you.

Why don't we take a couple questions at this point before we move to our final presentation.

Marc.