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Toward a Global Overview of HbA1c Test Performance

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Guests: Dr. Cas Weykamp is Director of MCA Laboratory of the Queen Beatrix Hospital in The Netherlands. Professor Eric Kilpatrick is the Division Chief in Clinical Biochemistry at Sidra Medicine in Qatar.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Although it may come as a surprise to most people including medical professionals, clinical laboratory test results often vary laboratory to laboratory, and patient care would be improved if the results were standardized. That simply means the same results regardless of factors like the location of the lab or the manufacturer of the test.

Test standardization is a complex and multifaceted effort that's remained a major goal for laboratory medicine's professional societies, including the AACC and IFCC. Hemoglobin A1c is an example of a test that has undergone global standardization due to its worldwide importance in diabetes screening, diagnosis, and care. A key part of any standardization effort is aligning all manufacturers' methods to an accepted reference method. This was the main aim of the European Hemoglobin A1c trial devised by the IFCC's Committee on Education and Use of Biomarkers in Diabetes.

The researchers investigated the performance of the hemoglobin A1c assays in more than 2,000 laboratories across 17 countries and 24 manufacturers. Results were evaluated per country, per manufacturer, and per manufacturer and country combined, according to criteria of the IFCC model for quality targets. The August 2018 issue of *Clinical Chemistry* includes an original research article that describes the European Hemoglobin A1c trial and its results.

We're joined in this podcast by one of the authors of the original article, and the author of an editorial that accompanied the article. Dr. Cas Weykamp is a Clinical Chemist and Director of MCA Laboratory of the Queen Beatrix Hospital in the Netherlands. He is also Network Coordinator of the IFCC Committee on Education on the Global Standardization of Hemoglobin A1c. Professor Eric Kilpatrick is the Division Chief in Clinical Biochemistry at Sidra Medicine in Qatar. He is professor of pathology and

laboratory medicine at Weill Cornell Medicine in Qatar, and also an Honorary Professor of Clinical Biochemistry at Hull York Medical School. He currently chairs the science committee of the European Federation of Clinical Chemistry and Laboratory Medicine. And one note here, Dr. Kilpatrick is joining this podcast via Skype; the sound quality of his audio is not the best, but we'll work with it as best we can.

So, Dr. Weykamp, let's start with you. What is the background of this trial?

Dr. Weykamp: Well, the background where every laboratory working for is to serve patients best and they can do it when the results are the same. Irrespective where you are in the world, so irrespective geographical area, or irrespective the test of any manufacturer used in any laboratory, results should be the same. When that is achieved, it is possible to have on a global scale, uniform reference values for interpretation and also uniform clinical decision limits, uniform clinical guidelines, and uniform quality goals.

This is a major goal of the International Federation of Clinical Chemistry and Laboratory Medicine, and derived from that goal, the reason for our IFCC committee to initiate this project, this EurA1c project, is that we want to see how laboratories in European countries succeed in achieving the same results. So, just the comparison of 2,000 laboratories, do get the same result from the same sample, that's the background.

Bob Barrett: And we'll go to you Dr. Kilpatrick, how can this be achieved?

Dr. Kilpatrick: Well, what we're talking about here is standardization and for that, laboratory professionals have developed a concept grandly called "metrological traceability."

Bob Barrett: That's an interesting term. Can you explain that, Dr. Weykamp?

Dr. Weykamp: Well, I won't go in details, but the bottom line is that all manufacturers anchor their diagnostic tests to a reference method. And once such an anchor test is used in all laboratories, patient outcome in all those laboratories is anchored as well to that reference method. In that way, the outcome in patient material should be the same everywhere in the world.

Bob Barrett: Well, that sounds fairly easy.

Dr. Weykamp: Yeah, like so many things, the concept is easy, yes. But to get there, in place, it is complicated. The reference methods should be developed and approved on a global

scale and then the transfer of the reference method to the diagnostic industry should be implemented.

Bob Barrett: And is this what you have done for Hemoglobin A1c?

Dr. Weykamp: Well, the answer is yes and no. Yes because we, and when I speak we, I talk about the IFCC, we have indeed developed and globally implemented a global anchor. The answer is no, because that it is not what this paper is about. So, once an anchor is in place as it is now, you want to know if it works, the "proof of the pudding." And that is what this paper is about. That is what we tested. Is HbA1c indeed standardized in daily life, in the field, in all the routine laboratories in Europe?

Bob Barrett: Dr. Kilpatrick, how do you test the success of standardization?

Dr. Kilpatrick: Well, different laboratories using tests from different manufacturers are asked to test their assay with the same sample, and we define optimum standardization as being when the results from all the laboratories are exactly the same. Now this isn't anything new within laboratory management. It's a standard procedure, and it's either called external quality assessment, or in United States, proficiency testing.

Bob Barrett: So, Dr. Weykamp, what is new in your work?

Dr. Weykamp: Well, proficiency testing is nearly always at a national level, and supplies information on the performance in the specific country. So, especially what you see in Europe that all countries have their own proficiency schemes, they have their own samples. So you can see performance in one country, in another country, and in another country, but it's often difficult to compare because there have been different samples.

Now, what would be ideal is that all those national organizers would use the same sample, then you can directly compare the performance, and that's what I tried to do. I asked national organizers in Europe to share the same sample and 17 of those organizations indeed agreed to do so. That's what I have done.

Bob Barrett: It sounds pretty much like "big data."

Dr. Weykamp: Yeah. I think that's true. At a national level, you might have 100 or 200 laboratories, but now we have more than 2,000 in those 17 countries, and to make the target value of those samples that we all used very reliable, I didn't have the true value assigned by one single reference laboratory, but five laboratories independently testing the sample and

assigning the true value to the sample. So, we have results of more than 2,000 laboratories.

Bob Barrett: Okay. So, Dr. Weykamp let's get right to it. What was the outcome of this trial?

Dr. Weykamp: Well, we interpreted the results using the model for quality targets we developed before, a few years ago. The basic concept of this model is that there are two major sources of error in the laboratory. One is that your calibration is not okay, then you get a biased systematic error, and the other is imprecision at random error. When you measure today, it can be different from tomorrow or even in the same run.

So, the model covers both sources of error, and then you can interpret the results of laboratories. And there are criteria in that model, and we found that 95% of the laboratories indeed met the quality criteria ,or you can also say 5% did not. But of course, with all these data, you can evaluate them all together or you can evaluate data across countries to see if there are differences per country, and also, across manufacturers of the diagnostic tests, and there we find substantial differences. These differences between countries and differences between manufacturers are highlighted in our paper.

Bob Barrett: Okay. So, where should I go when I want my Hemoglobin A1c tested?

Dr. Weykamp: Well, when we forget all subtleties, you should go to an island.

Bob Barrett: Okay. Well, where should I not go then?

Dr. Weykamp: Well, before I start talking an hour, if you want to know all that information, I suggest to read the paper including all the details and all subtleties. You can imagine, in a country where a test is used of the best manufacturer, well you will find out that the country performs well, and on the opposite when in the country a test is frequently used of a poor manufacturer, that country will perform poorly.

So, scientists never give a straightforward answer. They give a lot of data and you must make the conclusion yourself.

Bob Barrett: All right. Dr. Kilpatrick, on reading this, did the Hemoglobin A1c trial reveal any other interesting results?

Dr. Kilpatrick: Well, the design of the trial was such that the major source of error in all the countries could be identified. As we've had errors in the laboratory derived from two sources: the first is bias on the calibration side of things, and the second

is imprecision, which is a lack of reproducibility. What the study found was that the bias in the calibration was a minor source of error, and that's reassuring which is it means that standardization has been quite successful. It also means that the major source of error was that second source, namely imprecision, and now that's a target for manufacturers and laboratories, and that's what manufacturers and laboratories should be focusing on to improve quality. That is the reduction in between-laboratory variation.

Bob Barrett: So, let's look ahead. Dr. Weykamp, what is your perspective for the future of this?

Dr. Weykamp: Well, we, and when I speak on behalf of the IFCC, we want to repeat this trial every year to get to monitor how the quality goes on, if there is improvement. In fact, the second trial has been completed already and the third one is scheduled for October this year, and we have Eurocentric groups. That's how it got started. But through IFCC, we have contact with Latin America and Africa and we expect to have participation of these parts of the world as well.

And for Africa, it will only be a few laboratories, for they are developing and only top locations have HbA1c in place, but it can be your starting point for monitoring HbA1c in Africa. And although we pay a lot of attention to diabetes in the developed world, growth of diabetes can be expected in developing countries. When you look at the top 10 of countries where diabetes will occur in 10 years, you won't find any European country in it. It's India, it's China, it's Egypt, Saudi Arabia, Nigeria, South Africa, that are coming up.

So, although the number of these laboratories is still low, we feel as IFCC, we are worldwide organization, that we should go on with this and include those parts of the world.

Bob Barrett: So then would logistics be a big issue?

Dr. Weykamp: Yes it is. The most convenient sample to test in a laboratory is of course a fresh whole blood sample, but you can imagine when we ship fresh whole blood samples to Africa or Latin America and they are not shipped on cool packs or they are stuck on the way or at customs, it's not fresh whole blood anymore, it will be stinking and it's not okay. And to overcome that, we have developed a good alternative, it's a lyophilized hemolysate. It's freeze-dried whole blood. You can compare it with cup of soup, it's dry material. You can store it for a year and once you want soup, you simply add water and you have soup again. That's a process we also developed for blood. That means that we can also supply very stable material, very stable

samples to countries where their logistic system is not so good.

Bob Barrett: Well finally, Dr. Kilpatrick, given your column, you see a broader perspective?

Dr. Kilpatrick: Well for me, the point is that the study can be used as a template for other regions to develop similar operations, especially as we just had from Dr. Weykamp, the largest increases in the prevalence of diabetes are expected to occur in countries outside of Europe and outside of North America, such as Africa, the Middle East and Southeast Asia. So, perhaps a future aim should be to unite these groupings so as we have a global perspective, a global oversight of Hemoglobin A1c performance in the future.

Bob Barrett: That was Professor Eric Kilpatrick, the Division Chair in Clinical Biochemistry at Sidra Medicine in Qatar, he is also a Professor of Pathology in Laboratory Medicine at Weill Cornell Medicine, Qatar and an honorary professor of Clinical Biochemistry at Hull York Medical School.

Dr. Cas Weykamp is a Clinical Chemist and Director of the MCA Laboratory of the Queen Beatrix Hospital in the Netherlands. He also Network Coordinator of the IFCC Committee on Education on the Global Standardization of Hemoglobin A1c.

They have been our guests in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.