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The National Glycohemoglobin Standardization Program: Over 20 Years of Improving Hemoglobin A1c Measurement

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Guest: Dr. Randie Little is Coordinator of the National Glycohemoglobin Standardization Program.

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.

Measurement of hemoglobin A1c in blood is essential for the management of patients with diabetes mellitus. Hemoglobin A1c reflects the average blood glucose concentration over the proceeding 8 to 12 weeks. While the clinical value of hemoglobin A1c was initially limited by large differences in results among various methods, the investment of considerable effort to implement standardization has brought about a marked improvement in analysis.

In the July 2019 issue of *Clinical Chemistry*, a Review article chronicles the substantial progress that has been achieved in enhancing the accuracy of these measurements and the role of the National Glycohemoglobin Standardization Program in those efforts. Dr. Randie Little is Coordinator of the National Glycohemoglobin Standardization Program and co-author of that Review. She's also our guest in today's podcast. Dr. Little is a research professor in the Departments of Pathology and Anatomical Sciences and Child Health at the University of Missouri and is Director of the Diabetes Diagnostic Laboratory.

So, Dr. Little, what is the purpose of the National Glycohemoglobin Standardization Program and how has it changed over the years?

Dr. Randie Little: Well, the initial purpose of the NGSP was to standardize or harmonized hemoglobin A1c, so that results in routine clinical labs could be compared to those from landmark clinical studies, mainly the Diabetes Control and Complications Trial, or DCCT, and the United Kingdom Prospective Diabetes Study, or UKPDS. And also, so that they're comparable to treatment guidelines such as those from the ADA that came based on DCCT and UKPDS results. When the NGSP started, labs weren't even reporting the same thing. Some labs reported hemoglobin A1, some reported hemoglobin A1c, some reported total glycated hemoglobin, so the numbers varied widely just because they were reporting different fractions basically of glycated

hemoglobin. After A1c was basically standardized and all labs reported the same thing, reporting as hemoglobin A1c, the goal changed to improving measurement mainly by decreasing the variability of results among the labs.

Bob Barrett: How was the NGSP process of standardization different from the process for analytes that are being standardized today?

Dr. Randie Little: It's changed basically from a harmonization process to a very defined standardization process. Back in the '90s when we started the NGSP, there weren't any true reference methods available or pure reference materials. The method we used to trace our results back to was what would be called the comparative method, it was an HPLC system that was developed just prior to the DCCT. But there was a very important and immediate need to standardize results because of the clinical results from the studies that I've just mentioned. These studies showed that glycemic control made a huge difference in outcome for people with diabetes, and of course during those trials, glycemic control was measured using hemoglobin A1c.

The best model that we had at the time we started the NGSP was the CDC's program for cholesterol, which was a really good model for harmonization. But later in 2005, the EU or European Directive was implemented in Europe, of course, which stated that the traceability of values assigned to calibrators must be assured through available reference methods and reference materials of a higher order. That was kind of a vague statement and it took many years for people to really define what that meant and how it should be done. But today, there are a lot of true reference methods that use pure reference materials and they have developed traceability schemes, showing how clinical lab results can be traceable to higher order methods and materials.

So, when we attempted to standardize another analyte, this was C-peptide, manufacturers really are demanding all the pieces of the traceability chain, including reference materials and methods, and they want those methods and materials to be listed on the JCTLM website, that's the Joint Committee on Traceability and Live Medicine.

The standardization process today is much more complicated and time consuming than the process for harmonization, but that's what manufacturers are demanding. But back when we started the NGSP, there was a very immediate need and I think that is one of the things that made the program so successful.

Bob Barrett: Well, let's throw another acronym out there if we can. What are the differences between the IFCC and NGSP standardization programs for hemoglobin A1c?

Dr. Randie Little: Basically, after the NGSP was implemented, the IFCC developed true reference methods and certified some pure reference materials, they developed a network. The IFCC is following strictly the standardization process using these higher-level materials. So, even though the NGSP and IFCC are listed on the JCTLM database, the IFCC method is considered a higher order compared to NGSP, and it turns out there is an excellent linear correlation between NGSP and IFCC results, but the absolute values are not the same.

Since the NGSP was established prior to IFCC, most countries worldwide have aligned with NGSP, but now they were having to make a decision on whether to report IFCC results or NGSP results, and things got very confusing. But the NGSP and IFCC approaches are very different but they complement each other now. The IFCC ensures that manufacturers are traceable to an accuracy base following the EU directive, but there's no limit on the degree of the uncertainty or variability allowed between a manufacture's method and IFCC results.

In contrast, the NGSP defines acceptable limits per method performance based on clinical need. This is done through a certification program where manufacturer methods are certified as traceable to DCCT, KPDF results. As clinical need changes due to newer treatment strategies or increased use of A1c for diagnosis, the limits of acceptable A1c performance need to be, and has been tightened. We do this partly by tightening certification criteria. Also, we work closely with the College of American Pathologist to tighten their proficiency testing limits for hemoglobin A1c surveys.

As NGSP certification criteria have tightened so have the CAP criteria for passing. Basically, the IFCC program allows traceability and the NGSP tries to improve hemoglobin A1c measurement.

Bob Barrett: Why are these programs still important given the fact that hemoglobin A1c is basically already standardized?

Dr. Randie Little: Well, even though results basically match from different clinical labs, it's important that we decrease the variability among laboratories. And so, when we look at the CAP proficiency testing, we take all the results together, we can measure a coefficient of variation, for example. We can have a goal of decreasing variability among those labs. Even though results are basically the same, we have to set

some limits on how much variability we can allow among different methods in laboratories.

Bob Barrett: Well, finally doctor, talk about some of the current problems with hemoglobin A1c measurements?

Dr. Randie Little: Well, as we have improved hemoglobin A1c measurement, people have been more aware of different interferences. Even though for most patients with diabetes A1c is a useful indication of mean glycemia and risk for complications, there are some cases, sometimes it's a particular patient, sometimes it's a particular A1c method, but there are still some situations where hemoglobin A1c will not be accurate. Some interferences are due to biological differences or changes, and these might apply to all A1c methods, to measurement of A1c in general. This would include any condition that alters the survival of red blood cells, such as hemolytic anemia, also in later stages of chronic renal disease there's shortened red cell lifespan, or sickle cell disease where it lowers the red blood cell lifespan, and there are many other situations like that. So, physicians have to be aware and those conditions need to be well-defined.

There's also been some racial differences described but the reason for this is also not clear and the significance of that differences has not been clarified. And then there are some methods-specific hemoglobin variant interferences that need to be defined for each method. So, there's still a lot of work that needs to be done to further improve results and to define situations where hemoglobin A1c may not be accurate.

Bob Barrett: That was Dr. Randie Little, Coordinator of the National Glycohemoglobin Standardization Program. She has been our guest in this podcast on progress in glycohemoglobin standardization. Her Review with co-authors Curt Rohlfing and David Sacks on that topic appears in the July 2019 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.