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Harmonization of Test Results: What Are the Challenges; How Can We Make It Better?

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Guest:
Dr. Greg Miller is Professor in the Department of Pathology and the Director of Clinical Chemistry at Virginia Commonwealth University.

Bob Barrett: This is the podcast from *Clinical Chemistry*, I'm Bob Barrett. Laboratory test results are used to aid decisions in the diagnosis and treatment of disease. Consistent and comparable results from different measurement procedures are important for developing clinical practice guidelines, and for those guidelines to be applied to decisions about patient care. Yet results for many analytes are neither consistent nor comparable when measured using different clinical laboratory procedures. In the July 2014 issue of *Clinical Chemistry*, experts in harmonization of test results offered their opinions on the current state of the art and how we might make it better.

The moderator for the panel was Dr. Greg Miller. He's a Professor in the Department of Pathology and Director of Clinical Chemistry at Virginia Commonwealth University. He's our guest in today's podcast.

Dr. Miller, can you begin by explaining what harmonization means in the context of laboratory results.

Dr. Miller: Harmonization refers to the condition when a patient sample would have the same value if it were measured by all of the different methods that are in use for a particular analyte. A closely related term is standardization, which means that harmonization is achieved by having the calibration of all of the different methods traceable to a common reference measurement procedure. These two terms are frequently used interchangeably because they both mean that results are comparable among different measurement procedures. Harmonization is considered a more general term that includes standardization when the process is based on a reference measurement procedure.

Bob Barrett: So why is it important to have lab results that are harmonized when measured by different methods?

Dr. Miller: Well, clinical practice guidelines are commonly used and frequently base therapeutic decisions on fixed laboratory values. So if different methods give different results for the same sample, then we have errors in treatment of patients

that are possible. Clinical guidelines are frequently developed based on results using a single method in the central lab, but the problem occurs when these guidelines get into general use, they become less effective if different methods give different results. And physicians are generally not aware that different lab methods can give different values.

So the clinical laboratory community has a responsibility to ensure that results are consistent and can be compared irrespective of the method used. This is why having clinical laboratory experts as members of guideline development groups needs to be encouraged, so that measurement factors are considered when a guideline is developed.

Bob Barrett: It seems like harmonization of lab results is a basic requirement. Why are there differences in results when measured by different methods?

Dr. Miller: Well, there are only a small number of analytes that actually have reference measurement procedures with well-characterized reference materials used for calibration. Many of the analytes we measure in the lab are complex biomolecules for which there is no reference procedure. And when there are reference materials in many cases, they have not been developed to be commutable with clinical samples, which cause errors in calibration. And there are a lot of analytes that do not have any reference materials. So developers of procedures choose something available to use as a calibrator, but there's no uniformity in the materials chosen by different developers, so the results for patient samples are not harmonized.

In addition, the actual molecule measured by different assays may not be the same or it may not even be understood which molecular form of a biomarker is most important for its use in diagnosing or monitoring a clinical condition. Because of this, different methods give different results for what they think is the same molecule. A classic example is Troponin I which is a multiprotein complex whose composition changes in the course of a heart attack.

Bob Barrett: You mentioned commutability as an important property of reference materials; can you expand on just what that is and why that's important?

Dr. Miller: Sure. Commutability is a property of a reference material. That means it has reactivity characteristics that are the same as those for the biomolecule being measured in a clinical sample. More technically, commutability means that the numeric relationship between results from two or more measurement procedures is the same for clinical samples and for a reference material. Commutability is an important

property of a reference material because if there is a different numeric relationship for the reference material and the patient samples, then using that reference material as a common calibrator will actually make the results for the patient sample different between different routine methods.

Historically, the importance of commutability was not well-appreciated and so we have a number of a so-called reference materials being used as calibrators that are actually not commutable with patient samples. Fortunately, the importance of commutability is now generally recognized and developers of reference materials are now paying attention to commutability as an essential property to ensure the reference materials are suitable for use as common calibrators in a calibration traceability process.

Bob Barrett: Doctor, what tools are available for *in vitro* diagnostics companies to harmonize results from their measurement procedures?

Dr. Miller: There are several ISO standards that describe calibration traceability and what is required. And when a complete reference system is available, this includes a reference measurement procedure and a primary reference material for calibration, then manufacturers can fairly easily establish calibration to that reference system. However, the calibration traceability must be maintained for many lots of reagents, different lots of product calibrators, and different instrument platforms. These differences in details, in implementation, and how carefully a clinical laboratory uses a routine procedure will influence the consistency of results.

The situation becomes more complex when only a reference material is available for calibration, because of the commutability limitations we've discussed, issues with complexity of the biomarker, and limitations in the specificity of a routine method. Consequently, there is more variability among different routine methods when there is not a reliable reference measurement procedure.

Bob Barrett: Many laboratories develop their own measurement procedures, usually called Laboratory Developed Tests or LDTs. How can LDTs achieve harmonized results?

Dr. Miller: The issues regarding calibration traceability for LDTs are essentially the same as we've just been discussing. The main difference is that there are very few internationally recognized reference materials to use as common calibrators for the analytes measured using LDTs. As a result of that, different labs will use different calibrator preparations, and there's no consistency among them. So it's much more challenging to achieve harmonized results.

Bob Barrett: Are there regulations to consider in achieving harmonized results?

Dr. Miller: Yes. In many countries, there are regulations that clinical diagnostic tests must meet to be used for patient care. A major stimulus for harmonization came with the EU directive in 1998 that required any IVD product sold in Europe to have calibration traceable to higher order reference systems when these were available. So for lab tests entering the market, regulators are increasingly requiring conformance to any harmonization schemes that are generally accepted by the lab medicine community.

One of the challenges for harmonization is the cost to resubmit a regulatory approval to change the calibration traceability for an existing routine assay so that it will conform to any new national or international recommendations for harmonization. The cost is amplified for a multinational IVD manufacturer because the regulations are not uniform in different jurisdictions. So in many cases, the adjustment of calibration is really a simple linear factor, and the other characteristics of the assay remain the same. In this case, the relatively simple process for regulatory review should be suitable.

In other cases, more extensive changes in the assay are required, so there is not a one-size-fits-all approach for regulatory review. In any event, collaboration with regulatory bodies is an important part of our efforts to improve harmonization of laboratory results.

Bob Barrett: Well finally doctor, can you just summarize what the clinical laboratory community is doing to improve harmonization of test results.

Dr. Miller: Yes. In today's world, it's very important to recognize that harmonization activities occur on an international level, so we avoid national or regional differences in the agreement of results. The scientific division of the IFCC has for many years promoted standardization projects for a number of analytes, with considerable improvement and results harmonization. In fact, a lot of the reference measurement procedures we currently have available have been directly or indirectly stimulated by the work of the IFCC. But one of the big challenges has been a lack of an oversight body to prioritize the analytes that need to be harmonized and to coordinate the work of different organizations in different parts of the world that contribute to achieving harmonization for different analytes.

To address this situation, the AACC organized a conference in 2010, to identify and address the needs for harmonization. Based on the conference recommendations,

the AACC has initiated formation of a new international consortium for harmonization of clinical laboratory results. This consortium is now operational and has as its primary goals to prioritize analytes in need of harmonization based on their clinical impact and their use in guidelines, to provide a web portal to coordinate the work of different organizations to prevent duplication of effort, and to promote harmonization processes in particular for situations when there is not likely to be a reference measurement procedure developed.

Additional information on this program is available at the website www.harmonization.net.

Bob Barrett: Dr. Greg Miller is Professor in the Department of Pathology and the Director of Clinical Chemistry at Virginia Commonwealth University. He has been our guest in this podcast on harmonization of test results from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening!