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Harmonization: Its Time Has Come

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Guest:
Dr. Greg Miller is a professor of pathology at Virginia Commonwealth University in Richmond, Virginia.

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.

Though commonly underappreciated by the general public and even some healthcare providers, the importance of equivalency of laboratory test results across measurement procedures has a long history. The first proficiency testing results in 1947 demonstrated large discrepancies among results for the same measurand from different hospital laboratories, spurring decades' worth of on-going work to develop methods and regulations aimed at improving this situation. These efforts help to reduce potential for error in medical decision making, as standardization ensures results for a single analyte, measured by different procedures, are equivalent within medically meaningful limits. Standardization work has been slowed by technical difficulties that limit available reference materials and methods, which are both necessary for calibration traceability. In response, harmonization protocols have been proposed and developed to overcome these challenges of standardization and enable fit-for-purpose agreement among patient results.

The July 2017 issue of *Clinical Chemistry* includes a report of a carefully developed, step-wise approach to harmonize thyroid stimulating hormone results from 14 commercial measurement procedures. Dr. Greg Miller provided an editorial in this same issue, describing the culmination of this work and highlighting its importance. He joins us for this podcast. Dr. Miller is a Professor of Pathology at Virginia Commonwealth University, in Richmond, Virginia.

Dr. Greg Miller: The terms harmonization and standardization are both used to mean achieving equivalent results within medically meaningful limits among different measurement procedures for the same laboratory test. Traditionally, the term standardization has meant achieving equivalent results by having calibration traceable to a pure substance reference material to a reference measurement procedure or to a

matrix-based certified reference material. And harmonization has been used to describe a consensus process to achieve equivalent results among different measurement procedures when there are no suitable reference measurement procedures or certified reference materials available. However, recent discussion in the International Standard Organization, which I will refer to as ISO, a technical committee on clinical laboratory testing and in vitro diagnostic test systems, has suggested that standardization should be used as the more general term for achieving equivalent results and then harmonization is one of several possible approaches to achieve the condition of standardization so the terminology is evolving right as we are doing this podcast.

Now, harmonization or standardization of result is important because medical errors can be made when non-standardized results are used to make medical treatment decisions that are based on fix guidelines, or to assess changes in a medical condition for a patient.

Bob Barrett: Doctor, what infrastructure has been developed to support standardization of laboratory test results?

Dr. Greg Miller: Yeah, infrastructure is important and it has been evolving over a long period of time. You know, the importance of standardization has a long history. The first proficiency test occurred in 1947, and demonstrated large discrepancies among results from 59 hospitals in the Philadelphia area. Back in the 1950s to the early 70s, the AACC published a series of monographs titled "Standard Methods of Clinical Chemistry" that promoted using a single measurement procedure for measurand. This effort ultimately failed because technology and commercial interests, patent law, necessitated using different methods for the same test. So in 1977, a conference was organized by the CDC, the FDA and NIST, which gave us the United State National Reference System for the Clinical Laboratory. That program established the hierarchy of certified reference materials, reference measurement procedures, and reference laboratories that are now accepted as the highest order references for standardization of laboratory test results. About the same time, professional organizations and metrology institutes introduced matrix-based certified reference materials as the basis for calibration traceability of medical laboratory measurement procedures for measurands for which there were no reference measurement procedures.

Now, a landmark legislation in 1998 occurred in the European Union. They passed a regulation known as the EU Directive, that for the first time required calibration traceability to higher-order references whenever they were

available from medical laboratory measurement procedure sold in EU countries.

This legislation had an effective date of 2003 and recognized that nonequivalent laboratory test results contributed to errors in medical decision that affected patient outcomes. So, although the directive is only applicable to products sold in the European Union, the regulation had a global influence to improve standardization of results for medical laboratory measurement procedures worldwide.

Now, ISO responded to the EU directive by publishing its standard number 17511 in 2003. That standard specified requirements for calibration traceability to higher order references that included several levels of traceability depending on how complete a reference system existed for measuring. About the same time, ISO also published standards for certified reference materials, reference measurement procedures, and reference laboratories that provided testing services using reference measurement procedures. So at the same time, the early 2000s, cooperation among the International Bureau of Weights and Measures, the IFCC, and the International Laboratory Accreditation Cooperation established the Joint Committee for Traceability in Laboratory Medicine. This is referred to as the JCTLM. The JCTLM maintains a database of certified reference materials, reference measurement procedures, and reference laboratories that conformed to the ISO standards. Consequently, manufacturers of measurement procedures used the JCTLM listing to ensure the calibration traceability hierarchies they used will be compliant with the EU directive.

Now, the standardization principles included in ISO document 17511 have two practical limitations for implementation. One is that pure substance certified reference materials and reference measurement procedures do not exist and are not likely to be developed because of technical limitations for hundreds of important but complex measurands in laboratory medicine. The second limitation is that many matrix-based certified reference materials have not been validated to be commutable with patient samples, and in many cases have been shown not to be commutable and thus are not suitable for use in an ISO 17511 compliant calibration traceability hierarchy. In fact, tracing calibration to a non-commutable reference material will cause differences in results for the clinical samples when measured by different measurement procedures.

Bob Barrett: So what is being done to address the limitation, when no certified reference material or reference measurement procedure is available for a laboratory test?

Dr. Greg Miller: An international forum was organized by the AACC in 2010 to discuss challenges and recommend solutions for harmonization when there is no pure-substance certified reference material, reference measurement procedure or commutable, matrix-based certified reference material was available. One recommendation from the conference was to develop protocols for harmonization that provided consensus processes to achieve equivalent results when development of a reference measurement procedure was not technically feasible in a reasonable timeframe and commutable matrix-based reference materials were challenging or impossible to prepare.

So in the July issue of *Clinical Chemistry*, Linda Thienpont and colleagues from the IFCC Committee for Standardization of Thyroid Function Tests report phase IV in a series of reports that have developed the science behind a process for harmonization of thyroid stimulating hormone results from 14 different commercial measurement procedures. Essential to this harmonization protocol were panels of authentic individual serum samples that fill the role of harmonization reference materials. The key advantage of using panels of individual samples is commutability issues do not influence their use as harmonization reference materials for calibration traceability. Although sample specific influences may exist in an individual sample, the effects can be identified and addressed by the statistical data analysis approaches. The protocol used in this report, used the all procedures trimmed mean for each individual patient sample to develop the recalibration algorithms applied by each commercial producer of a measurement procedure.

So among the technical challenges in this work was developing an approach to sustain the harmonization over time since a limited volume of the panel of individual samples was available. The authors developed a separate panel of clinical samples prepared to the same specifications that were value assigned in the same experiment with the phase IV panel. This continuation panel serves the role to sustain the recalibration process in subsequent steps as well as to provide a link to the original recalibration panel when preparing subsequent panels.

So the final key component of the harmonization protocol is surveillance of continued harmonization over time among results from the measurement procedures. The report proposes to monitor harmonization over time using a patient sample results based feedback program developed separately by Dr. Thienpont's research team. Another approach to surveillance could be proficiency testing or external quality assessment using commutable samples.

Bob Barrett: Finally doctor, how can harmonization protocol be recognized and implemented by manufacturers of medical laboratory measurement procedures?

Dr. Greg Miller: Well, the International Consortium for Harmonization of Clinical Laboratory Results recognized the importance of harmonization protocols as one of the levels of calibration traceability hierarchy recognized by ISO. So, a proposal was submitted and approved by ISO Technical Committee 212 to begin development of a new standard identified as ISO/NP (new project) 21151 with a title *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for international harmonization protocols intended to establish metrological traceability of values assigned to product (end user) calibrators and human samples.*

So, when this new standard is published, harmonization protocols can be listed by JCTLM to enable their use by manufacturers of measurement procedures to achieve harmonized results among different measurement procedures from different manufacturers for the same measurand. So this report of a successful harmonization protocol by Dr. Thienpont and her colleagues is important to laboratory medicine because it demonstrate a practical approach to achieve equivalent results when pure-substance certified reference materials, reference measurement procedures, or commutable matrix-based certified reference materials are not available or not likely to be available due to technical limitations. I recommend you read the full report from the IFCC committee. Thank you very much.

Bob Barrett: Dr. Greg Miller is a professor of pathology at Virginia Commonwealth University in Richmond, Virginia. He has been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.