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# Harmonization Status of Serum Ferritin Measurements and Implications for Use as Marker of Iron-Related Disorders

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**Guest:** Dr. Sara Pasqualetti from the Clinical Pathology Unit of the University Hospital, Luigi Sacco in Milan, Italy.

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.

The concentrations of ferritin circulating in the bloodstream reflect the amount of intracellular ferritin, the main iron storage protein in humans. So, the measurement of serum ferritin is used extensively for the diagnosis of iron-related disorders. In the last two decades, most studies have considered low concentrations of serum ferritin as the diagnostic standard for iron deficiency, replacing the invasive bone marrow aspirate examination. Increased serum ferritin concentrations are observed in patients with body iron overload of any cause including hereditary hemochromatosis. However, data on the comparability of results among commercial measuring systems for ferritin are contradictory.

A paper appearing in the September 2022 issue of *Clinical Chemistry* concluded that harmonization among methods for measuring ferritin is far from optimal with the implementation of traceability to different WHO standards being a factor.

To discuss the implication of these findings, we are happy to have the author of that study with us in this podcast. She is Dr. Sara Pasqualetti, Section Supervisor at the Clinical Pathology Unit of the University Hospital, Luigi Sacco in Milan, Italy.

So, first of all, Dr. Pasqualetti, what are the main points that your study in *Clinical Chemistry* have uncovered?

Sara Pasqualetti: Okay so, serum ferritin is a marker extensively used for the diagnosis of iron-related disorders. And given the recommendation of common diagnostic decision limits present in all major clinical practice guidelines, harmonization among the commercial methods measuring the protein is devoted for correct results interpretation independently of the analytical system employed for the analysis, but contradictory data are available in literature. Therefore, so our study [aimed] to investigate the inter-assay variability, meaning, the harmonization status -- measurements of

harmonization status, among the way they will use the measuring systems currently available in the market.

The inter-assay variability among measuring systems was verified by performing correlation studies among different systems on a panel of human serums pools reasonably behaving as clinical sample tested in daily practice.

The study showed a relatively large inter-assay variability with the median inter-assay coefficients of variation of 23%. This inter-assay variability strongly impacted the clinical classification of patients as we presented in the paper.

We also assessed the trueness of calibration possibility of such evaluated systems by testing the recovery of WHO third International Standard for ferritin. But unfortunately, the recovery of this standard was influenced by its substantial noncommutability for two systems, in particular Abbott and Roche systems. On the other end, the third International Standard of the WHO for ferritin was commutable for user only with Beckman Access and Siemens Centaur, but Access being the only measuring system correctly recovering its assigned value.

This results question the possible use of this material, this reference, this international standard material as the common calibrator of commercial assay within projects adding [as aim] the improvement of methods of harmonization.

Bob Barrett: So, doctor, what obstacles are expected in the case of the lack of a suitable reference material, which is central in the measurement of harmonization project?

Sara Pasqualetti: Okay. So, this is a didactic example showing as the non-commutability of a reference material proposed for common calibration of commercial system may affect clinical samples' results.

Commutability is a property indicating how well a reference material mimics the characteristics of clinical sample in a measuring system for a stated measurand. When assessing commutability for a given material, the results obtained by two measuring systems should show closeness of agreement with the results for clinical sample tested within the same analytical run. When non-commutable materials are used as reference calibrators, bias value can be assigned to commercial calibrators that may result in too much great variability among assays.

In the past, the importance of commutability characteristic of reference material was underestimated, but now, both IFCC

and CLSI are working hard to increase the awareness of reference material providers about this issue.

For instance, the new revision of the CLSI EP30 document on the characterization and quantification of commutable reference materials for laboratory medicine, which is now in the last stage of standard development, is clearly focusing on the importance of the commutability assessment.

Bob Barrett: What value does the study add to the current status of knowledge about ferritin measurement?

Sara Pasqualetti: Maybe the most important results of our study is that related to the implication for ferritin used as marker of iron-related disorders. Using a simulation approach, the clinical impact derived from the lack of harmonization of the ferritin measurements was investigated. As previously discussed, the effective application of clinical guidelines for iron metabolism disorders and for the use of common decision limits for diagnosis and therapeutic intervention, irrespective of the measuring system employed for the analysis, relies on measurements harmonization and on the interchangeability of the results among the different measuring systems.

So, in our study, we showed that the lack of measurements of harmonization among 4 widely used commercial methods for ferritin caused different classification of the same clinical samples at each considered iron deficiency anemia cutoff.

The Figure 1 in the paper illustrates of course this outcome, and this finding indicates that the current situation of ferritin measurements common thresholds for iron efficiency anemia detection cannot be used until four methods-dependent cutoff would be required. But the good news is that throughout a simple mathematical recalibration by using data from regression equations obtained by comparing the other assay[s] to the Beckman Access, harmonization of the ferritin results was possible. Reducing the inter-assay coefficients of variation from 23% to approximately 5%, henceforth allowing the use of common decision thresholds.

Results obtained by this measuring system, the only one for which the third International Standards for ferritin of WHO mentioned, was commutable and correctly recovered, could be indeed used as surrogate reference for correct implementing metrological traceability to these standards. And this Figure 15 in the supplemental material in the paper shows the harmonization in diagnostic classification of clinical samples after this recalibration.

Bob Barrett: Well, in conclusion, Doctor, what strategies can be proposed to achieve an effective ferritin measurement harmonization?

Sara Pasqualetti: Okay, so, we can distinguish different strategies depending on the time needed for the [evaluation.] The first, the immediate strategy, could be to use the evidence provided by our study about the regression parameters obtained from the comparison between ferritin values by each measuring system in the Beckman Access target values and correcting the results of ferritin assays, making them unbiased by a simple recalibration approach, as discussed before.

The proposed use of a proprietary assay as a surrogate reference could represent a practical approach for improving the comparability of ferritin results among analytical systems in a short term.

The second strategy is applicable at medium long-term. The provision of a commutable reference material to be used as a common calibrator can be expected. Unfortunately, WHO is continuing to provide the new International Standard for ferritin without assessing the commutability affecting the theoretical principles behind the release.

Bob Barrett: That was Dr. Sara Pasqualetti, Section Supervisor at the Clinical Pathology Unit of the University Hospital, Luigi Sacco and the Research Center for Metrological Traceability in Laboratory Medicine in Milan, Italy.

She has been our guest in this podcast on harmonization status of serum ferritin measurements and their implications for use as a marker of iron-related disorders. She is the co-author of a paper on that topic that appears in the September 2022 issue of *Clinical Chemistry*.

I'm Bob Barrett. Thanks for listening.