

*Ortho-Clinical Diagnostics offers the following reply:*

*To the Editor:*

Interference by hemoglobin is clearly labeled in the VITROS® Troponin I assay's "Instructions For Use" and Package Insert. The hemoglobin concentrations used and the differences measured are stated under "Limitations of the Procedure" (1).

Our upper reference limit (URL) study used a total of 768 fresh heparin-plasma samples from healthy individuals, which were collected at four different centers and tested with the VITROS Troponin I assay to establish a reference interval for healthy individuals and to validate the product claims in the Package Insert and Instructions For Use. No samples were excluded because of hemolysis, and only two samples (0.25%) were above the URL of 0.08 µg/L (ng/mL).

The incidence of hemolyzed samples in Dr. Hawkins' study appears to be higher than our experience based on our customer service records. A hemoglobin concentration of 1000 mg/L (100 mg/dL) causes substantial discoloration of the sample, which can be easily observed by most laboratory technicians and therefore flagged for potential interferences.

We recommend that customers continue to use the cutoffs stated in our labeling for the VITROS Troponin I, i.e., 0.08 µg/L as the URL and 0.4 µg/L as the cutoff for acute myocardial infarction. Use of the cutoff of 0.22 µg/L suggested by the author may lead to false negatives, which are clearly less desirable from a medical point of view than the false positives that may result from a small number of greatly hemolyzed samples that have not been excluded by good laboratory practice.

#### Reference

1. Ortho-Clinical Diagnostics. VITROS Immunodiagnostic Products Troponin I Reagent Pack. Instructions for use. Publication No. J03812, Ver.

3.0. Raritan, NJ: Ortho-Clinical Diagnostics, December 11, 2002:9.

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#### Reliability of IFCC Method for Lactate Dehydrogenase in Heparin Plasma

*To the Editor:*

I wish to clarify the statement in our report (1) that the Roche lactate dehydrogenase (LD) method "does not provide reliable results" in heparin plasma. The report showed a problem observed only during primary-tube sampling from heparin-plasma tubes from Becton Dickinson. Serum and EDTA plasma caused no problems, suggesting that the method otherwise performed well.

We became aware of data from another laboratory that used Sarstedt sampling tubes and that showed none of the errors we had reported. From additional experiments (manuscript in preparation), we believe that the previously reported errors might be eliminated by adding a predilution step in the analytical sequence. This predilution step now is included in the IFCC method from Roche.

#### Reference

1. Bakker AJ, Mirchi B, Dijkstra JT, Reitsma F, Syperda H, Zijlstra A. IFCC method for lactate dehydrogenase measurement in heparin plasma is unreliable. *Clin Chem* 2003;49:662-4.

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#### Mass Spectrometry-based Diagnostics: The Upcoming Revolution in Disease Detection Has Already Arrived

*To the Editor:*

I read with great interest the editorial entitled "Mass Spectrometry-based Diagnostics: The Upcoming Revolution in Disease Detection" by Petricoin and Liotta (1). These authors provided provocative commentary on current and new mass spectrometry (MS)-based approaches in clinical chemistry related to detection and characterization of various diseases, with emphasis on proteomics and cancer diagnostics. They discuss MS as disruptive or nonlinear because of the excitement and fear that are generated by its use. The editorial correctly implies that the potential contributions of MS in clinical chemistry are staggering.

I suggest that these authors have a somewhat narrow view of MS applications in clinical chemistry limited to their area of expertise. Furthermore, I would disagree somewhat with the statement that MS-based approaches are disruptive and nonlinear. Petricoin and Liotta omitted the extensive historic role of MS in clinical chemistry, including the numerous contributions and advancements in the previous two decades. Bruns et al. accurately describe the recent and important contributions of mass spectrometry and included timely manuscripts in the text, *Molecular Testing in Laboratory Medicine* (2). Dozens of other articles have appeared in *Clinical Chemistry* and other journals regarding MS applications in clinical chemistry, as evidenced in surveys of the literature that I and others have written recently (3, 4).

The purpose of this letter is not to detract from the importance of the editorial or its content, but rather to perhaps provide the reader with a few more important ideas and to

remind the authors of the editorial as well as the reader that MS is not new and has already made a substantial impact in clinical chemistry. The authors are correct in that introduction of MS has created some fear in those who do not understand it and the new approaches to analysis, although I would not call the process disruptive. I am one of the champions of introducing MS in the clinical laboratory, but I am also a champion of caution and the "rules" by which clinical chemistry is performed. As a mass spectrometrist by training and a clinical chemist by practice, I have learned that equally important to new technologic methods are issues related to quality control, standardization, specimen choice and collection, result interpretation, patient follow-up, and genetic counseling/education. Publication of a method in clinical chemistry is only the first step in acceptance and utilization of a new approach. The issue of cost-effectiveness through high-throughput multianalyte screening is evidenced by the success of tandem MS-based analysis in newborn screening, by which nearly one-half of the infants born in the US will be tested in the next 1 or 2 years.

Those of us who participated in this renaissance of MS in clinical chemistry realized that diagnostics and screening are much more than an analytical result. More than a dozen years after introducing mass spectrometric approaches to newborn screening, we are still developing improved quality assurance and quality control, improving technology, educating physicians and patients, and finding that MS is not always the best method available. Clearly, those endeavoring to introduce new state-of-the-art methods would be well served by reviewing contributions of MS already published, many of them in clinical chemistry (Note that this

issue alone contains three articles pertaining to MS). It is important to keep in mind that a mass spectrometer is simply a detector, albeit a versatile and powerful one. It is how it is used and what information it provides to the clinical chemist that makes it the successful system it is. I do not think that MS engenders fear but rather that it generates excitement and healthy discussion on the future of clinical methods.

#### References

1. Petricoin EF, Liotta LA. Mass spectrometry-based diagnostics: the upcoming revolution in disease detection. *Clin Chem* 2003;49:533-4.
2. Bruns DE, Lo YMD, Wittwer C, eds. Molecular testing in laboratory medicine: selections from *Clinical Chemistry*, 1998-2001, with annotations and updates. Washington, DC: AACC Press, 2002:361pp.
3. Chace DH. Mass spectrometry in the clinical laboratory. *Chem Rev* 2001;101:445-77.
4. Chace DH, Kalas TA, Naylor EW. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. *Annu Rev Genomics Hum Genet* 2002;3:17-45.

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*Drs. Petricoin and Liotta respond:*

*To the Editor:*

The use of mass spectrometry in the clinic is occurring and having a profound impact in specific applications. As Dr. Chace correctly points out, mass spectrometry is being used with fantastic success for neonatal screening and metabolic disorders, and he and others have led and continue to lead this effort. This bodes well for the eventual acceptance for more broad use

of mass spectrometry for other routine diagnostic testing applications.

We disagree, however, that our view is too narrow. Rather, quite to the contrary, what we are proposing is not a narrow view of the current state but one of a vision forward: a future where a revolution in clinical diagnostics could lead to the widespread use of mass spectrometry and where the mass spectrometer is the dominating clinical analyzer for both proteomics and genomics. This revolution would be sparked not from looking for smoking gun differences in known metabolites; in this instance, you know what you are looking for, and the mass spectrometer is measuring it.

The revolution in clinical diagnostics that we are referring to will come when mass spectrometry is successfully married with advanced pattern-recognition algorithms that hunt for multiple markers simultaneously and then use these patterns as the diagnostic readout itself. The use of proteomic pattern diagnostics can have profound implications because it does not require one to know the identity of each component ahead of time.

Much work remains to show that this method works reproducibly in a clinical setting and to have it accepted by the scientific community. There is a need for additional publications, editorials, and commentaries showing and discussing the merits, limitations, and utility of proteomic pattern analysis with other applications, using small study sets so that the field can gain momentum and allow scientific vetting and discourse. We are moving forward, however, to evaluate and transition this method to the clinic as quickly as possible.

The most rigorous evaluation we have is a Food and Drug Administration approval process with formal clinical trials. Therefore, our strategy as US Public Health Scientists is to

use this most rigorous process for our upcoming National Cancer Institute-based trial for ovarian cancer detection because it serves two immediate and cross-cutting purposes: advancing this to patient benefit as quickly as possible while testing it with the highest scientific rigor.

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