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Clinical Implications of a Recent Adjustment to the High-Sensitivity Cardiac Troponin T Assay: User Beware

To the Editor:

Roche Diagnostics recently issued a technical bulletin calling for an

adjustment to the calibration curve for the Elecsys Troponin T hs and Elecsys Troponin T hs STAT assays. Although this bulletin was disseminated widely in some countries, it was less widely distributed in others. The Roche high-sensitivity (hs) assays are in clinical use worldwide except within the US, where they are used for research but have not yet been cleared by the Food and Drug Administration. Roche has characterized this action as a “minor adjustment” to the low-end standardization of the Troponin T hs assays in order to return to the original assay specifications. The new revised lots (numbers 167345 and 167650) yield measurable cardiac troponin T concentrations in hs assays in a greater proportion of patient samples for which the concentrations were undetectable with previous lots [163704 (Troponin T hs) and 164773 (Troponin T hs STAT)] and older lots (6 lots total). Specifically, Roche has indicated that the new lots will produce higher recoveries at low concentrations (3–20 ng/L) and produce a shift upward—as much as +7 ng/L at concentrations of 3–8 ng/L and up to +5 ng/L at concentrations of 8–20 ng/L. Unfortunately, no correlation studies that compare earlier lots against the new lots are available. Thus, no information is available regarding what shifts may have occurred above the 20-ng/L value.

The implications of this calibration reformulation and the questions it raises are many. First, what will be the effect of the reformulation on the well-established 99th percentile value of 14 ng/L that has consistently been reported in the literature? Second, what percentage increase in detectable results will be seen among patients presenting for emergency care? Third, how does this change affect findings from the hundreds of published studies that have used both the 99th percentile value and δ changes over time to examine diagnostic ac-

curacy, and how does it change the findings for risk stratification of acute coronary syndrome patients and apparently healthy patients? Fourth, what mechanisms are in place to alleviate customers' concerns that similar product adjustments for this hs assay that have substantial downstream implications for patient triage and management will not occur in the future? Fifth, does the new reformulated calibration curve permit recalculation of the concentrations that have already been published in the current literature? The answers to these questions are essential for customers trying to interpret the relationship of previous data to new data.

The occurrence of this problem is not surprising, considering the challenges presented by the quality assurance of hs assays. We have been perplexed by the fact that early data suggested that most healthy individuals have detectable values. In the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) study (1), 97.7% of participants had a value above the limit of detection, which was 1 pg/mL (1 ng/L) at the time with a precommercial assay. In the original validation by Giannitsis et al. (2), 80% of putatively healthy participants had values above the limit of the blank. By the time of the large international cooperative study, however, only 57% of putative healthy study participants had values above the limit of the blank, and only 32% had values above the limit of detection (3). This percentage fell even further, with only 25% above this limit in a community-based study (4). In addition, the original diagnostic study (1) found that the hs assay for cardiac troponin T did not detect more myocardial infarctions than conventional assays (5). Was this decrease due to the change now reported by Roche, or did some other change occur very early in the assay?

We believe that these findings have major implications for patient

care. We urge that in addition to correcting the lot issues it has defined, Roche reevaluate (at a minimum) subsets of the key research sample sets to ensure that: (a) there is no need to recalculate the 99th percentile value that is the cornerstone of the Universal Definition of Myocardial Infarction, and (b) the data upon which the metrics proposed for the use of this assay are correct. Such a reevaluation should be conducted immediately with appropriate clarifications, as necessary, in the journals in which the index reports were published. We strongly encourage editors of all journals to ensure that all submitted manuscripts in this area identify the lot of reagent used and that authors be able to document that the presented data reflect the reformulated, new-calibration lots.

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CH-8 Phenotype in Steroid 21-Hydroxylase Deficiency: Fact or Fancy?

To the Editor:

The defective *CYP21A2*¹ (cytochrome P450, family 21, subfamily

A, polypeptide 2) genes downstream of the *TNXB* (tenascin XB) gene in congenital adrenal hyperplasia (CAH)² fall into 3 categories: (a) small-scale conversions from the *CYP21A1P* (cytochrome P450, family 21, subfamily A, polypeptide 1 pseudogene) gene, (b) spontaneous mutations, and (c) chimeric *RCCX* modules that include the chimeric *CYP21A1P/CYP21A2* genes and chimeric genes of *TNXA* [tenascin XA (pseudogene)] and *TNXB* (1). Most of the *CYP21A2* mutations of the 15 loci identified thus far are due to small-scale conversions from *CYP21A1P* during both meiosis and mitosis (2). These mutations account for approximately 70% to 80% of CAH cases. These 15 mutational loci include nucleotide (nt) -126 (C>T), nt -113 (G>A), nt -110 (T>C), nt -103 (A>G), P30L, nt 655 (A/C>G), nt 707-714del, I172N, cluster E6 (I236N, V236E, and M239K), V281L, F306AL307insT, Q318X, and R356W. The chimeric *CYP21A1P/CYP21A2* and *TNXA/TNXB* genes, which are caused by unequal crossing over (or deletions) during meiosis (2) and occur in approximately 20% of CAH alleles in most populations (1, 3) reflect, respectively, the deletion of the 1/*XCYP21A1P-TNXA-RP2-C4B-1/XCYP21A2* gene array [where 1/*X* indicates an uncertain fraction of the gene sequence, *RP2* is the retinitis pigmentosa 1 pseudogene (serine/threonine kinase 19) located on chromosome 6, and *C4B* is the complement component 4B (Chido blood group) gene] (1) and a deletion of the *RP2-C4B-CYP21A2-1/XTNXB* gene array (1).

family A, polypeptide 1 pseudogene; *TNXA*, tenascin XA (pseudogene); *RP2*, pseudogene of retinitis pigmentosa 1 pseudogene; *C4B*, complement component 4B (Chido blood group).

² Nonstandard abbreviations: CAH, congenital adrenal hyperplasia; nt, nucleotide(s); 1/*X*, uncertain fraction of the gene sequence.

¹ Human genes: *CYP21A2*, cytochrome P450, family 21, subfamily A, polypeptide 2; *TNXB*, tenascin XB; *CYP21A1P*, cytochrome P450, family 21, sub-