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Analysis of patient results distributions to reevaluate a reference range change for calcium, after a change in assay reagents on the Roche Cobas c500 analyzer

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A change in reagents for calcium (Ca) on the Roche Cobas c500 used in our laboratory analyzer took place in 2013. The previous reference range (8.5-10.5 mg/dL) was replaced with that from the manufacturer’s study (8.6-10.0 mg/dL), based on correlation of results between the new and old assays. As a matter of quality assurance, we undertook a post-assay-change reevaluation of the reference range change, using a method based on that of Bhattacharya [1]. In short, the method relies on the assumption that the reference range is a normal distribution, which assumption enables this distribution to be isolated mathematically from within all-comers patient distribution data that are not normally distributed.

**METHODS AND RESULTS**

Primary data were all patient Ca results retrieved for a one-month interval (Figure 1). Isolation of the data subset compatible with a normal distribution was a two-stage process: The point of maximum slope of the cumulative patient results distribution was determined to define the mean/median of the embedded normal distribution (9.4 mg/dL; Figure 2).

For each of these intervals, an iterative search was made to determine the central fraction of a normal distribution encompassed by each interval, as evidenced by the linearity of a normality plot when the correct fraction was specified (Figure 4).

Varying widths of intervals of results having symmetry around this midpoint (a necessary condition for a normal distribution) were assigned for analysis (Figure 3).

The reference range from Figure 5 data was essentially identical (±0.1 mg/dL) to “textbook” reference ranges (e.g., [2]). A comparison of the patient results distribution to the reference range distribution is shown in Figure 6.

The results were used to update our Ca reference range. Normal distribution analysis of patient data subsets by this method can be a powerful tool to evaluate reference ranges, simply because it can include a large number of patients using retrospective data. In comparison, identification and testing of “normal” patients in similar numbers would be difficult or impractical. In particular, clinical verification of a normal population for Ca would be expensive for any large number of patients, involving combined evaluation of Ca, renal function, vitamin D status, and PTH. These results demonstrate that one can have reasonable confidence in an esoteric method for extraction of a reference range from an all-comers patient results distribution. The related method of Hoffman [3] is more well-known but less stringent, being applied with varying degrees of success in recent literature [4–7].