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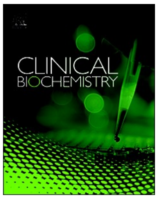

Letter to the Editor

Correct implementation of the Hoffmann method

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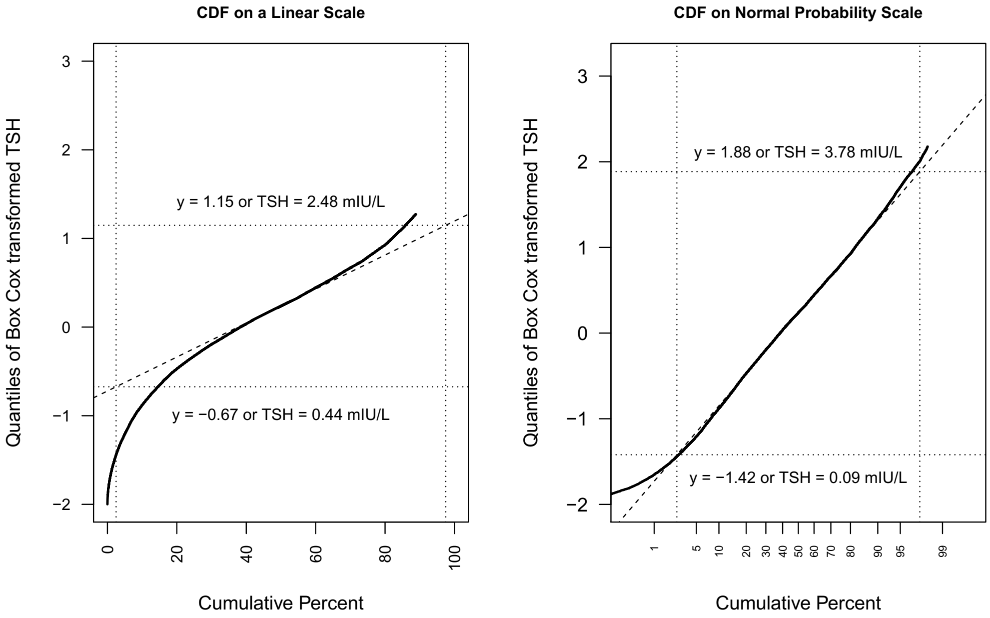
To the Editor,

I read with interest the recent paper from Zhang et al. outlining the limitations of the Hoffmann method [1]. The authors' primary finding is that the method produces unexpectedly narrow reference interval estimates. To mitigate this, they elaborate on a previously proposed strategy [2,3] of extending the range of test results used in the Hoffmann method (beyond the obviously linear region) to improve estimates of the lower and upper limits of normal. Appropriately, the authors perform a normalizing transformation to allow the data to better conform to the required assumption that the empirical distribution is a Gaussian mixture [4]. However, it appears from Fig. 1 of their paper that they have not followed Hoffmann's mandatory prescription to prepare a cumulative distribution function (CDF) plot in *normal probability space* (or equivalently a normal Q-Q plot) as evidenced by the linear spacing of the cumulative percentages on the *x*-axis. This is an understandable error as it has frequently been made in the past [5]. However, the error explains why the authors' Hoffmann analysis produced unexpectedly narrow reference intervals. The correct approach obviates the need for an *ad hoc* improvement strategy.

Elsewhere, it has been shown that the use of a standard CDF in attempting Hoffmann's method produces unpredictable reference interval estimates unrelated to the true values in a predictable way except to say that they are generally too narrow [5]. Even in the simplest


CDF on a Linear Scale

CDF on Normal Probability Scale

Fig. 1. Comparison of CDFs of Box Cox transformed synthetic TSH data prepared in linear scale (left) and normal probability scale (right). Vertical dotted lines represent the 2.5th and 97.5th percentiles. Horizontal dotted lines represent the lower and upper normal range estimates based on extension of the linear mid-portion of the CDF (dashed lines).

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possible scenario of a pure Gaussian distribution of healthy individuals, the use of a linear CDF will generate reference interval estimates of $\mu \pm (1 - \alpha)\sqrt{\frac{\pi}{2}}\sigma = \mu \pm 1.19\sigma$ whereas the Hoffmann procedure as originally described [4] will generate the expected results of $\mu \pm 1.96\sigma$, for $\alpha = 0.05$. In this case, the variant procedure will define the central 77% of the distribution rather than the central 95% which by and large explains the authors' findings.

To illustrate this point, using the R statistical programming language, 100,000 synthetic TSH results were generated in the distribution implied by the histogram shown in Fig. 3 of Zhang's paper. The frequency table was reconstructed using the open-source tool G3data. After Box Cox transformation (optimized to $\lambda = 0.5$) a linear CDF similar to Zhang's Fig. 1 can be produced. In contrast, the CDF in normal probability space has a much different appearance (see Fig. 1 of this letter). Performing a Hoffmann procedure using a standard CDF (without efforts to extend the region defined as "linear") generates an approximate normal range of 0.44–2.48 mIU/L while performing the Hoffmann method in normal probability space yields a wider estimate of 0.09–3.78 mIU/L.

The incorrect approach sets another trap in that a standard CDF nearly always has a region of apparent linearity by virtue of the sigmoidal shape of CDF functions. However, the linear mid-portion of the CDF has no particular utility to address the problem of indirect reference interval estimation [5]. The strategy of heuristically extending the "range of linearity" of the Hoffmann method shown by the authors and others [2,3] merely serves to offset the error of deviating from Hoffmann's original procedure.

Modern maximum likelihood strategies exist for mixture model decomposition beyond the graphical methods of Bhattacharya and Hoffmann which should be considered given the availability of open-source computational tools for that purpose [5].

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