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LETTER TO THE EDITOR

Critical Appraisal of Personalized Reference Intervals

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Dear Editors,

We read with great interest the article by Demirelce et al. which proposes the use of personalized reference intervals (prRI) as a novel approach to interpreting hematology laboratory results [1]. We agree that population-based reference intervals (popRI) suffer from important limitations (as illustrated by the ferritin reference range: a serum ferritin concentration of less than 30 μg/L has a high specificity and sensitivity for diagnosing iron deficiency in adults, but many laboratories reported lower limits of normal [2]). However, we would like to draw the attention of the readers of the *International Journal of Laboratory Medicine* that the implementation of prRI raises significant clinical, ethical, methodological, and economic concerns.

The study of Demirelce et al. [1] concludes that prRI should be implemented in routine laboratory practice to improve result interpretation and patient safety, yet the methodology described actually requires strict inclusion criteria for control subjects, that are, absence of known disease, good health status, and no relevant ongoing treatment. This necessitates a prior medical evaluation and five consecutive blood samplings in each healthy control. Such requirements raise ethical and economic challenges. Ethically, it is difficult to justify subjecting healthy individuals to repeated blood sampling solely for the purpose of establishing prRI values, and impossible in vulnerable populations such as children [3]. Economically, it is unlikely that the healthcare system will reimburse the analysis of these repeated blood samples, meaning that healthy patients will have to pay for these tests themselves. Furthermore, the clinical evaluation of these patients would represent an unjustified consumption of medical resources. This runs counter to current initiatives aimed at reducing costs and promoting the appropriate prescription of tests [4].

On review of the original paper, the inclusion of control subjects with hemoglobin values falling outside both population-based reference intervals (popRI) and WHO's reference interval [5] is particularly concerning, as illustrated by female participants 35, 80, and 91 (hemoglobin <120 g/L) and male participants 11 (hemoglobin <130 g/L) and 13 (hemoglobin >180 g/L). Such deviations strongly suggest the presence of underlying pathological or constitutional conditions, including iron deficiency anemia, chronic blood loss, dietary factors, autoimmune diseases, intense physical activity, high-altitude exposure, or heavy smoking, and therefore warrant further clinical investigation. This risk is further amplified by limitations in the statistical handling of outliers, as the Dixon Q test can identify only a single mathematically defined outlier without clinical validation. As a result, values flagged as outliers may either represent an individual's true physiological baseline (thus meriting inclusion in prRI calculations) or reflect transient or underlying pathological conditions. These cases underscore the necessity of an additional control step whereby any personal reference interval (prRI) must remain within established popRI or, at a minimum,

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within internationally published reference intervals. Deviations must be explicitly justified to avoid the normalization of pathological states.

Interpretation is further compromised by the absence of information on the timing of sample collection for the prRI cohort, which prevents appropriate contextualization of outliers and increases the likelihood that clinically significant abnormalities may be overlooked. Relatedly, while the popRI was derived from data collected over 6 months, no comparable information is provided for prRI sampling. It remains unclear whether the five required measurements per individual were collected over a similar timeframe, at consistent intervals, or over a much shorter period, a distinction that is critical given that measurements obtained over consecutive days are unlikely to yield the same prRI as those distributed across several months.

Beyond sampling considerations, the long-term validity of prRI is also questionable and raises important concerns regarding longitudinal validity and sampling methodology, as the study does not adequately address how physiological variability over time is accounted for. Physiological variations that may occur over longer periods (such as those following the cessation of maternal feeding or exclusive breastfeeding, during growth phases, at menarche, during pregnancy, or at menopause) or other life-stage–related changes can substantially alter an individual's homeostatic set point [6, 7]. The authors do not provide any guidance on whether or when prRI should be reassessed in response to such changes.

Understanding these longitudinal concerns is further complicated by the nature of biological variation (BV), describing the variation observed in the concentration of different constituents in a person. BV is regulated by homeostatic processes and, in a steady state, typically manifests as random variation around a homeostatic set point [8]. However, as previously noted, this steady state can be disrupted by life-stage changes. Such variations not only challenge the long-term validity of metrics such as prRIs but also highlight the need for robust methodological frameworks capable of accounting for this biological dynamism. In particular, the estimation of analytical and personal coefficients of variation (CVa and CVp, respectively) must adequately reflect these complexities to ensure clinical relevance and reliability [9]. In the present study, CVa and CVp were estimated from repeated measurements of the same samples without any precision regarding the methodology, raising concerns that the same data may have been used both to estimate variability and to define the prRI.

Finally, the clinical relevance of using prRI must be questioned. On one hand, the interpretation of some hematological parameters like hemoglobin (anemia: $<120\,g/L$ for a women [5]) and platelet count (different platelet transfusion thresholds across different clinical settings [10]) is more a matter of clinical pathology thresholds than reference ranges. On the other hand, the clinical impact of this personalized adjustment in terms of morbidity and mortality should be evaluated.

Overall, these limitations call into question the clinical added value of personal reference ranges as they are currently proposed, suggesting that their systematic application in clinical practice is premature. Important analytical concepts, such as measurement uncertainty (MU), determined in the majority of laboratories with internal and external quality controls [11], and reference change value (RCV), calculated using analytical and intra-individual coefficients of variation and assessing whether two values differ significantly in biological terms [12], appear to be more effective in improving the interpretation of results. Measurement uncertainty is particularly useful when reliable reference values are unavailable or when results are close to clinical decision thresholds (e.g., reticulocyte count due to lack of standardization [13] or platelet count relative to transfusion thresholds). Measurement uncertainty and reference change values are also useful for comparing results and assessing whether a significant analytical (MU) or biological (RCV) difference exists between them.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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