Editorial

Interpretation of laboratory results: the Reference Intervals, a necessary evil?

Assistance with interpretation of laboratory tests is one of the major concerns of laboratorians; therefore, an appropriate presentation of laboratory reports is essential. Accompanying results with Reference Values (or Reference Intervals) for quantitative analytes aims to help the clinician (and the laboratorian) to interpret laboratory results. This concept of Reference Values, born in the 1970s under the impetus of Ralph Gräsbeck and a Scandinavian Working Group, is generally accepted by the professional communities and the official bodies (1–3). Following European Directive 98/79/CE, manufacturers must state Reference Intervals on the Package Insert of laboratory reagent kits (4). The Clinical and Laboratory Standards Institute (CLSI) thus decided in 2005 to revise its document (C28-A2) devoted to determination of Reference Intervals, in cooperation with a dedicated Committee of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (5).

The original concept of Reference Values does not solve all the questions of presentation of laboratory results for optimized interpretation, and many additional methodological and/or conceptual articles are regularly published in scientific journals. A special issue of this journal was recently devoted to this subject (6).

The IFCC philosophy, taken up by the CLSI and manufacturers, proposed the near exclusive use of Reference Limits on laboratory reports as a guide for interpretation. The principal advantage of this position is its clarity: it clearly differentiates Reference Limits (or Intervals), as purely descriptive of a well-defined population (closest to the patient), from Decision Limits. The IFCC (and the CLSI) state very firmly that Decision Limits are different, because “they are based on other scientific and medical knowledge and they may be related to a specific medical condition” (5). On the other hand, Reference Intervals are calculated by different statistical methods (parametric or non-parametric) from a reference sample defined as an adequate number of persons selected for testing on the basis of well-defined criteria (exclusion and partition) and of an appropriate questionnaire. This concept of Reference Intervals is misunderstood by clinicians: they do not accept a statistical definition, but prefer the notion of Decision Limits. The limits of the use of Reference Intervals as a tool for interpreting laboratory results are quickly reached. For some years, there has been an evolution to replace some Reference Intervals by Decision Levels determined by a consensus of the medical community and/or Scientific Societies based on clinical evidence linking such Decision Levels with clinical outcomes. To date, the tests involved are rare (e.g., hemoglobin A1C, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol...). Moreover, the existence of several Decision Limits adapted to different clinical cases does not simplify the presentation of laboratory reports.

On the other hand, determining Reference Intervals remains particularly complex, time-consuming and costly. Most laboratories give up. Reference Intervals cannot be readily transferred because they are dependent on the analytical systems used (very few of which have proper standardization and traceability) and the reference population for which they were determined. The challenges in transferring Reference Intervals also apply to transferring Decision Limits, although this is less often recognized in daily practice.

In this issue of *Clinical Chemistry and Laboratory Medicine*, two articles by Haeckel et al., the start of an announced series, try to bring concrete solutions and new light on this problem (7, 8). The first article of the series is clear and educational (7). However, the authors have chosen a purely methodological approach that is noticeably statistical. On the conceptual level this approach can be justified, but may be confusing for the average reader. The prospective model is set against the unimodal approach (traditional concept of Reference Intervals) and the bimodal approach (Decision Limits concept). This manner of presentation could induce some confusion in the mind of the reader, since they are two quite different and supplementary approaches. Collecting both under the same title does not seem appropriate. The retrospective model is better adapted and the authors demonstrate its advantages. There are fewer ethical problems and this is important when the difficulties in recruiting volunteers are more and more important with the current legal and regulatory reinforcement of privacy and autonomic rights. The model is also less expensive. However, the authors do not emphasize sufficiently the selection criteria for the reference population: their approach implies a very well organized database, containing all the relevant clinical and biological information. Unfortunately, this is rarely the case. One point on which they are very credible is the question of Internal Limits vs. External Limits. They are also correct in stating the difficulties in transferring Reference Intervals and Decision Limits. It is right to point out that European Directive 98/79/EC places all the responsibility on the manufacturer for proposing reference intervals. This is why the proposal of Haeckel et al. in favor of the determination of intra-
laboratory Reference Intervals is challenging and is one possible solution. However, this cannot be considered as the only solution. It necessitates extensive resources, notably the ready availability of a consistent database to allow implementation of the required selection criteria. The limits of such an approach appear obvious in reading their second article (8). The observed differences between laboratories’ Reference Intervals are attributed to the population, but could, among other things, be due to inappropriate selection of the reference population. Nevertheless, they are to be commended for this interesting research approach, although it is only applicable to large laboratories.

Another approach to try to solve the transference problem was initiated by the IFCC and the CLSI, with the active support of manufacturers, on the one hand, by proposing to laboratorians several simple and practical solutions for evaluating the transference of Reference Intervals as proposed by the manufacturers in their package insert and/or from data in the literature, and on the other hand, by asking manufacturers to put at the user’s disposal detailed conditions used for determination of the Reference Intervals, e.g., pre-analytical conditions, criteria for selection of reference sample, life habits, ethnic origin, etc. The great merit of this pragmatic approach is that it is simple, reliable and highly practicable for all clinical laboratories.

We need to recognize the challenging aspect of these articles by Haeckel et al. Reference Intervals have for more than 35 years made a valuable contribution to the interpretation of laboratory results. One could say they are at minimum an acceptable solution in helping the clinician to locate an observed laboratory value. However, all the development and research on the subject should be guided by the final use and the final user, who is most often the clinician. Most of the scientific work published in recent years has been connected to methodological and statistical problems. Perhaps the real question to be asked is: what is the added value for the clinician of the Reference Intervals printed in laboratory reports in comparison with Decision Limits that are well adapted to a defined clinical situation and to a given patient?

Laboratory professionals should give greater importance to a pragmatic approach. Haeckel et al. are right to emphasize that it is no longer reasonable to spend vast amounts of money on determining Reference Intervals at a time when health expenses must be optimized. We still do not have the answer as to what is the most efficient method to achieve this objective.

To their credit, we must acknowledge that Haeckel et al. make laboratory professionals aware of their responsibilities to advance the role of the laboratory in defining Reference Intervals. But we should not delude ourselves; the proposed methodology necessitates extensive technical resources to collect clinical information and to conduct statistical data treatment. This is not within the capability of all laboratories. The proposal of the IFCC, recognized by the scientific community and by manufacturers for many years, rests on a standardized approach (analytical system, selection of population and statistical calculation of Reference Intervals). A simple method for evaluating the transference of Reference Intervals produced by manufacturers and/or from the scientific literature has also been proposed.

In conclusion, it is highly likely that the use of Reference Intervals and the presentation of laboratory results will evolve in the next few years. However, it should be allowed to proceed gradually in a structured fashion:

1. Respecting the terminology and the definitions for Reference Intervals, Reference Limits and Decision Limits that are proposed by the IFCC and are internationally recognized (9). Those do not invite confusion and are likely to stand the test of time.
2. Welcoming all new proposals on the methodological level both for the determination of Reference Intervals and for defining Decision Limits. Nevertheless, these must bring something more practical, more reliable and more efficient for clinical laboratories. If not, this will be a purely speculative contribution. The proposals should be within the resources of all laboratories, independent of their size.
3. Optimizing the presentation of laboratory reports by improvement of their clinical informative content, particularly for Reference Intervals. Although this is one of the most promising ways, it will require difficult and complex work.

While waiting for conclusive progress concerning these last two items, it would be better advised to retain the experience from the work of the IFCC. The current recommendations would then advance following future clinically relevant research. To promote such research it could be suggested that laboratorians reinforce their partnerships, on one hand with manufacturers for implementing analytical traceability and standardization, and on the other with clinicians for the determination of Decision Limits. This topic is highly controversial and it would be very productive and highly desirable that this series of articles would give rise to numerous comments and suggestions to this journal in letters to the editor and/or scientific articles.

References


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