Biologic Variation Approach to Daily Laboratory

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KEYWORDS

• Biological variation • Error limits • Quality control • Reference change value

KEY POINTS

- Biologic variation is an unavoidable result of the continuous changes inherent in a living organism and has been studied within subject and between subjects.
- Biologic variation can be used to set the analytical performance specifications for total allowable error, imprecision, and bias (trueness).
- Biologic variation can also be used to assess the significance of changes in serial patient results through a reference change value.
- Biologic variation can be used to determine rules to help autoverification of patient results.
- Recent conferences and studies have made important observations about the validity and usefulness of today's biologic variation estimates. An international effort is working toward improving these estimates.

INTRODUCTION

Laboratory medicine is the science that gives information on the patient health status on the basis of measurements of biological fluids. It is well-known that concentration of analytes in these fluids are not the always exactly at the same concentration owing to the simple fact of being a living, constantly changing organism; this is what in general is named biological variation (BV). Characterization and understanding of BV enables a valid assessment of the significance of a laboratory result.

There are many sources of BV that have been very well-described,[1] with random variation around a central value the focus of this article. There are 2 components of

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random BV: within-subject BV and between-subject BV. Within-subject BV is the random variation around the homeostatic setting point[1] or the random variation that assures an equilibrium state of the human body (data not published[2]). Between-subject BV is the variation among the central points of different individuals. Both terms are usually expressed in terms of percentage coefficient of variation (intraindividual coefficient of variation [CV_I] and intragroup coefficient of variation, respectively).[3]

The way to estimate the components of BV was thoroughly described by Fraser and Harris[4] and data on BV have been compiled in a BV database since 1999 (Ricós-Stockholm conference).[5] This database has been updated every 2 years by the Analytical Committee of the Spanish Society of Clinical Chemistry and Molecular Pathology (SEQC) and has been regularly published at the Westgard website.[6]

More recently, some weaknesses of this database have been described, such as the lack of published studies available for an important number of analytes, discrepancies among the papers that have been compiled, and so on[7,8]; these points were discussed at the European Federation of Clinical Chemistry and Laboratory Medicine Milan Strategic Conference where a Task and Finish group was created with the aim to improve the current database and transform it to a more comprehensive and granulated one as well as reliable as reference data. All the information compiled may be available and will no longer merely the list of quality specifications, but also supporting data such as confidence intervals, and so on.[2,9]

USES OF BIOLOGICAL VARIATION

The currently available data on BV are important information for the medical laboratory that may be used for different applications. These are (1) setting analytical quality specifications, also named performance quality specifications, which are mainly used within the laboratory, (2) assessing the significance of changes in serial results from an individual, reference change value (RCV) that can be used both intralaboratory (delta-check) and can be shown to the clinicians in the laboratory report to inform them about significant changes in patient health status (RCV), and (3) autoverification of results.

Analytical Quality Specifications

Since the Aspen conference in 1977,[10] it has been an accepted standard that the analytical coefficient of variation should be maintained below one-half of the within-subject CV, so that the amount of variability added to the true variability of the result is only about 10%.[11] Further, Gowans stated that when bias is limited below one-quarter of the within-subject plus between-subject coefficients of variation, only a limited percentage of results should be falsely considered outside the upper and lower limits of the population-based reference interval.[12] Accordingly, Ricós and colleagues[13] suggested a limit for total allowable error (TAE) for a single measurement based on the combination of both criteria. The formulae that summarize these statements are:

$$CV_A \leq 0.5 * CV_I$$

$$\text{Bias} \leq 0.25 * (CV_I^2 + CV_G^2)^{1/2}$$

$$\text{TAE} \leq 1.65 * 0.5 * CV_I + 0.25 * (CV_I^2 + CV_G^2)^{1/2}$$

Although the formula for TAE has been debated[14] and some alternatives have been proposed, no revised formula has been generally accepted to date. From the first