SYMPOSIUM 1 - New approaches for deriving and applying biological variation data for clinical use

BIOLOGICAL VARIATION – RECENT DEVELOPMENTS AND FUTURE CHALLENGES

A.K. Aarsand [1]
[1]*Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Bergen, Norway*

Biological variation refers to the natural fluctuation that is observed in the concentration or activity of a measurand within an individual, reflecting the regulation of homeostatic processes in the body. There are many laboratory applications that utilize biological variation data, including to set analytical performance specifications and to aid in the interpretation of laboratory test results. For the latter purpose, biological variation data are used to calculate reference change values, to define personalized reference intervals, to derive population-based reference intervals and to estimate the index of individuality. Thus, it is important to recognize that biological variation data are reference data, and that the validity of biological variation based analytical performance specifications and other applications depends on data being robust and relevant to the setting and population to which they are applied. In the last decade, there have been a number of advances aiming to improve the quality of available biological variation data, with a particular focus on addressing heterogeneity in study designs and statistical analyses. These include new models and approaches to deliver biological variation components, a critical appraisal checklist and other standards for deriving and reporting biological variation data and the development of the EFLM Biological Variation Database, which delivers quality-assessed data with automatically calculated biological variation applications to users worldwide. As of today, robust data are still lacking for many measurands, population groups and settings, and further work is required to address how biological variation data can best be applied to improve diagnosing and monitoring of patients.

SYMPOSIUM 1 - New approaches for deriving and applying biological variation data for clinical use

DEALING WITH BIOLOGICAL VARIATION IN SPORTS DRUG TESTING - THE ATHLETE BIOLOGICAL PASSPORT APPROACH

T. Piper [1], M. Thevis [1]
[1]*Institute of Biochemistry - Center for Preventive Doping Research, German Sport University Cologne, Cologne, Germany*

In 2009 the World Anti-Doping Agency (WADA) started the Athlete Biological Passport (ABP) program introducing the Hematological Module by monitoring selected markers in blood over time to detect doping practises. Based on the successful implementation with more than 300 athletes sanctioned in the first 5 years, WADA introduced the Steroidal Module of the ABP in 2014. Here the concentrations and concentration ratios of six urinary steroids are monitored in order to detect the misuse of testosterone (T) or T-prohormones. Especially the ratio of T/epitestosterone proved to be a sensitive marker for doping.
Due to some shortcomings especially in the passport evaluation of female athletes, WADA broadened the scope for steroids including serum concentrations of T and 4-androstenedione in 2023. At that time also, the Endocrine Module focussing on hGH doping was introduced.
All these models are based on the same Bayesian statistical approach relying on reference population-based initial thresholds for each marker under investigation. The first sample collected from an athlete is assessed against these thresholds, for all subsequent samples the thresholds are adopted according to the individual values found. This approach significantly increases both the sensitivity and specificity already with the third sample collected.
The calculated thresholds represent a combination of the individual biological variation associated with each marker and the overall measurement uncertainty harmonized by WADA for all doping control laboratories world-wide.
One of the main challenges for Athlete Passport Management Units evaluating each passport is the potential influence of confounding factors like ethanol for the Steroidal or altitude training for the Hematological Module. These confounding variables necessitate further investigations into each suspicious sample before considering an outlier as an atypical passport finding.

SYMPOSIUM 1 - New approaches for deriving and applying biological variation data for clinical use

NEW MODELS FOR BIOLOGICAL VARIATION DATA AND CONSEQUENCES FOR THEIR PRACTICAL USE

S. Sandberg [1]

[1]*The Norwegian Organisation for Quality Improvement of Laboratory Examinations (Noklus), Haraldsplass Deaconess Hospital, Bergen, Norway*

Biological variation (BV) data have many applications in laboratory medicine. However, these depend on the availability of relevant and robust BV data fit for purpose. BV data can be obtained through di#erent study designs, both by experimental studies and studies utilizing previously analysed routine results derived from laboratory databases. The di#erent BV applications include using BV data for setting analytical performance specifications (APS), to calculate reference change values (RCV), to define the index of individuality and to establish personalized reference intervals.
There are many models to set APS based on BV. The APS used should take into account the intended use of the APS and in what circumstances it should be used. APS for imprecision and for measurement uncertainty are in principle purely based on BV. Models for bias and total allowable error are based on a combination of the BV model (type II) and the indirect outcome (type 1b) model. A new model will be presented for minimum, desirable and optimum APS. The RCV indicates the probability (given by a Z value) that results outside the RCV is caused by other factors than analytical and biological variation. An app to calculate the RCV is given on the EFLM website on BV (https://biologicalvariation.eu). Recent research on which factors to take into account when using RCV will be presented. In the lecture, the newer aspects of the practical use of BV will be elaborated.

SYMPOSIUM 1 - New approaches for deriving and applying biological variation data for clinical use

USING BIOLOGICAL VARIATION DATA TO DEFINE PERSONALIZED AND POPULATION-BASED REFERENCE INTERVALS

A. Coskun [1]
[1]*Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey*

Interpretation of laboratory data is a comparative process that requires reliable reference data for accurate medical decision-making. Currently, reference intervals (RIs) used in the interpretation of patients' laboratory data are derived from population data, based on single measurement results from samples taken from at least 120 reference individuals. Although alternative approaches, such as using patient data, are possible, the quality of such data is often suboptimal. The requirement of at least 120 reference individuals, reliance on single measurement results, and omission of natural biological variation (BV) in analytes make it challenging for laboratories to implement their own RIs and impact their reliability. To enhance the accuracy of patient laboratory data interpretation, RIs should be personalized, incorporating the BV of analytes in their estimation.

For a given analyte, BV data consist of two key components: (i) between-subject BV (CVG), which represents the variability in analyte set points among different individuals, and (ii) within-subject/person BV (CVI/P), which denotes fluctuations in analyte levels around the set point. While CVI is estimated from data collected across a group of individuals, CVP is derived from repeated measurements within the same person. These components serve as valuable data sources for establishing both personalized and population-based reference intervals.

Personalized reference intervals can be estimated from an individual's set point, derived from the average of repeated measurements, and CVI/P.

Similar to personalized reference intervals, population-based reference intervals can be estimated from the population set point, which is derived from the average of single measurement results from a few reference individuals, along with CVI and CVG.

It can be concluded that BV data is a powerful tool for estimating both personalized and population-based reference intervals. For population-based reference intervals, utilizing BV data requires only a small number of reference individuals (approximately 16), compared to the 120 required in conventional methods. Moreover, by accounting for the natural variation of the analyte, this approach enhances the reliability of RIs in laboratory data interpretation.