Editorial

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Biological variation – eight years after the 1st Strategic Conference of EFLM

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Biological variation (BV) is one of the most important sources contributing to uncertainty in laboratory examinations and should be taken into account in any interpretation made. There are many sources of BV [1]. In this special issue, we focus primarily on the within-subject BV (CV_i), defined as the variation of a measurand around its homeostatic set point in an individual in a steady state condition. This concept was introduced by Schneider already in the 1960 [2]. It has been further developed and addressed by major figures in the field such Per Hyltoft Petersen, Callum Fraser, Carmen Ricos, and others, to whom the whole laboratory community is grateful [3]. Estimates of CV_i are used for many purposes in laboratory- and clinical medicine, and applications such as index of individuality (II), reference change values (RCVs), personalized reference intervals and setting analytical performance specifications (APS) are some examples [1]. The role of BV in setting APS was addressed in the Stockholm conference in 1999 [4] and later in the 1st EFLM Strategic Conference in 2014 [5]. In the 1st EFLM Strategic Conference, the consensus agreement was that three models could be used

to set APS: the first model based on clinical outcomes, the second on BV, and the third on state-of-the-art [6]. In conjunction with the Strategic Conference, it was recognized that much of the available BV data were hampered with uncertainty or not fit for purpose, and that there was a need for critical appraisal of existing BV data as well as for new studies to generate high-quality data [7]. After the conference, a Task Force was established, consisting of five different Task and Finish Groups (TFG) addressing the different aspects raised in the conference [5]. The terms of reference for the TFG on the Biological Variation Database (BVD) included to “develop a critical appraisal list to evaluate literature on BV and extract essential information from the papers as well as summarizing the selected information on a database on the EFLM website” [5]. Later this group was transformed to a Task Group and embedded in the EFLM Working Group on BV (WG-BV) [8]. Presently, about 20 persons representing 10 different countries, also from outside Europe, are working with BV in EFLM. Their work, with some initiatives starting already before the Strategic Conference, has resulted in four major achievements:

- (1) New mathematical models to calculate BV estimates were developed [9–12] by Thomas Røraas, to whom this special issue is dedicated.
- (2) A standard for evaluating BV publications, the Biological Variation Data Critical Appraisal Checklist (BIVAC) was developed and published in 2018 [13].
- (3) The European Biological Variation Study (EuBIVAS) was initiated by the WG-BV [14]. The EuBIVAS is a highly powered study, including 91 volunteers from five European countries and, benefiting from the Røraas methods, has delivered new high-quality BV data for a high number of measurands, as summarized in ref. [15].
- (4) The establishment of the EFLM BVD [16] which presently contains nearly 3,000 BV data records for 240 different measurands, derived from more than 550 papers. The EFLM database also provides global BV estimates based on systematic reviews and meta-analysis of quality-assessed studies [17–26] and is an ongoing work, where all new papers on BV are being appraised and included in the database.

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The increased activity in this field also has generated renewed interest in BV worldwide. Though many historical BV studies were performed according to the standards at the time, more recently published BV studies comply with the BIVAC, as illustrated by the papers included in this issue. On the methodological front, new ways of estimating BV such as using a Bayesian approach [12] and extracting “big” data from laboratory information systems [27] have been outlined, and these approaches are being further developed. New applications of BV data have also emerged, such as deriving personalized reference intervals for an individual, based on estimates of CV_I and previous test results from a steady state situation [28].

This special issue contains, following an open invitation from the CCLM, papers from members of the WG-BV, the TG-BVD as well other authors and includes both original papers and reviews, covering a wide range of measurands and BV related topics.

Systematic reviews and meta-analysis of published BV data, appraising studies from both healthy and unhealthy populations and different sampling intervals, are included for kidney-related measurands [22], thyroid related measurands [18], trace elements [25], and tumor markers [29]. These reviews highlight the need for more high-quality data for many, less studies measurands and states of health, to allow for a better understanding of BV in disease and application of these data. Data from the EuBIVAS have resulted in three original papers, on thyroid related measurands [30], insulin [21], and tumor markers [31]. This issue also includes a summary paper of the EuBIVAS [15], as well as a new original study, which addresses interesting aspects of the EuBIVAS population considering multivariate information applying machine learning algorithms [32]. In addition, there are original studies, based on a prospective study design reporting on the BV of kidney-related markers [33], trace elements [34], serum neurofilament light chain [35], cardiac myosin binding protein C [36], GDF-15 [37], anti-Müllerian hormone [38], and hematology measurands [39]. BV data for clinical chemistry parameters in the population subgroup of athletes are also presented [40]. Furthermore, statistical aspects related to personalized reference intervals [28] are addressed [41]. It is important also to include limitations in the application of BV data and this has been done in a letter [42], related to the use of BV data for RCVs for tumor markers.

In the coming years, the science and art of BV will be further developed, including hopefully delivery of new methods for deriving BV data. As an example, an interesting paper comparing four methods of indirect data-mining approaches to calculate BV is included in this issue [43]. The utility of BV data will be expanded into new areas

such as for personalized reference intervals and machine learning taking advantage of new technologies. It is also important that we are better at communicating the degree of uncertainty in BV data and that this must be taken into account when the data are used, for example, to calculate RCV and APS.

New approaches for setting APS based on BV data are under development and will be presented on the 5th Cutting Edge in Laboratory Medicine (CELME) conference in Prague, scheduled for the 2023, where the topic of APS will be re-addressed nine years after the 1st EFLM Strategic Conference.

Thomas Røraas was a mathematician who in his doctoral thesis [44], modestly entitled “Estimating Biological Variation – Methodological and Statistical Aspects”, presented his three landmark papers [9–11], addressing new mathematical considerations on how to handle BV data and how to plan BV studies including power calculations. These considerations have been used as basis for a lot of the BV work published in recent years. He further expanded the field by introducing a Bayesian approach [12] to deriving BV data. Thomas was an essential and much valued member of the WG-BV and TG-BVD. In contrast to many of us, Thomas was not interested in publishing as many papers as possible. He was not interested in doing “routine” science, but to be able to allocate time for thinking and to develop new ideas. He was a perfectionist and an idealist in an imperfect world. Thomas died in October 2020, 42 years of age.

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