Letter to the Editor

The European Biological Variation Study (EuBIVAS): delivery of updated biological variation estimates, a project by the Working Group on Biological Variation in the European Federation of Clinical Chemistry and Laboratory Medicine

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Provenance: This is a Letter to the Editor Commissioned by the Section Editor Bo Tang (IVD Business Unit, Vazyme Biotech Co., Ltd., Nanjing, China).

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We were really honored by the recent editorial written by Prof. Fraser (1) about biological variation (BV) as a comment on our paper, published in Clinical Chemistry, reporting new BV estimates for nine enzymes (2) based on samples from the European Biological Variation Study (EuBIVAS) (3).

This study on enzymes is just the first outcome of a large project, the EuBIVAS, that originated from the need of overcoming the concerns of the quality of the data available in published BV studies (1,4) and consequently the reliability of some of the BV data included in the current on-line database (5). To obtain reliable BV data is demanding because it requires the involvement of many individuals and a large number of blood collections to provide adequate power, as demonstrated by Røraas *et al.* (6).

When, in 2013, I joined the Working Group on Biological Variation (WG-BV) of the EFLM (7) I had the opportunity to share with all the other members the idea, born in San Raffaele, to organize a large study involving several European countries, to collect a relevant number of samples to be able to verify or re-define estimates of BV for a great number of measurands. The opportunity to collect samples from apparently healthy subjects from different countries was very attractive, but also hazardous because the possibility of introducing a significant pre-analytical variability, thus invalidating all the effort.

To minimize this risk, taking account of all the requirements of the EFLM checklist for BV studies (8), a very detailed protocol was prepared and agreed upon.

This EuBIVAS protocol (3), rigorously followed by each involved laboratory for all steps, as well the dedication and care of all the people involved in the project, have been the keys for the success of our work. The mean values of the clinical chemistry measurements performed until now, calculated with confidence intervals, obtained from the enrolled healthy individuals from the different European countries, are in fact perfectly overlapped and there is no data indicating any differences in pre-analytical variables or treatment between the different laboratories. The only exception was serum creatinine in Turkey, but in this case the difference is related to a real difference in the population, as recently published (9). Thus, the BV estimates obtained from EuBIVAS samples are widely applicable and can be used to determine analytical quality specification (APS) at an international level.

The first set of measurements, performed on serum samples using ADVIA 2400 Siemens instrument, included the most common components in clinical chemistry. All

data have been elaborated and some of them have been already published (2,9), while others are under preparation (electrolytes, lipids and some substrates).

The main finding of the first step of EuBIVAS measurements is that most of within-subject BV (CV_I) and between-subject BV (CV_G) estimates are lower than those reported in the current on-line database, and, consequently, also the APS derived from them.

The second finding is that, for some measurands, significant differences between mean values in subgroups [i.e., males /females; female menopause/fertile age; or for creatinine Turkish people (2,9)] were found. When the mean value of a subgroup is significantly different from the other(s), the lowest CV_G from the different subgroups was used to calculate APS.

The next set of measurements in line, still in progress, are coagulation tests [routine coagulation tests (APTT, PT, fibrinogen), coagulation inhibitors (antithrombin, protein C chromogenic, and protein S free) and D-Dimer] on plasma citrate samples, using ACL TOP 750 instrument (Instrumentation Laboratory, A Werfen Company). For hemostasis variables, samples handling tests needs detailed precaution (i.e., sample thawing at 37 °C) to ensure the stability of the samples, and, in fact, information on BV is still limited and is based on small studies with a limited number of sampling points, a short time period, and/or only specifically selected parameters (10).

The third step of EuBIVAS project involves specific proteins and immunochemistry and will be performed on a Cobas 8000 modular analyzer (module c702 and e801), Roche Diagnostic. The measurements are planned for the end of 2017.

Thus, the EuBIVAS will, on a short time scale, deliver reliable BV data for a large number of measurands. This is important for several reasons, especially for the definition of sound APS. APS are the basis for the development and evaluation of new analytical systems and for setting criteria of acceptability of internal quality control results and proficiency testing.

Prof. Fraser writes "*Moreover, it is hoped that the use of the checklist for new studies would stimulate researchers, authors, reviewers, and journal editors to ensure that studies deliver robust estimates of within-subject and between subject biological variation*" and reports as excellent example our results obtained for nine enzymes activities (1). The EFLM WG-BV is working for the EuBIVAS project to represent a real benefit in improving BV estimates currently available for as many measurands as possible.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Fraser CG. Biological variation: a rapidly evolving aspect of laboratory medicine. J Lab Precis Med 2017;2:35.
2. Carobene A, Røraas T, Sølvik UØ, et al. Biological Variation Estimates Obtained from 91 Healthy Study Participants for 9 Enzymes in Serum. Clin Chem. 2017;63:1141-50.
3. Carobene A, Strollo M, Jonker N, et al. Sample collections from healthy volunteers for biological variation estimates' update: a new project undertaken by the Working Group on Biological Variation established by the European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2016;54:1599-608.
4. Carobene A. Reliability of biological variation data available in an online database: need for improvement. Clin Chem Lab Med 2015;53:871-7.
5. Minchinela J, Ricós C, Perich C, et al. Biological variation database and quality specifications for imprecision, bias and total error (desirable and minimum). The 2014 update. Available online: http://www.westgard.com/biodatabase-2014-update.htm
6. Røraas T, Petersen PH, Sandberg S. Confidence intervals and power calculations for within-person biological variation: effect of analytical imprecision, number of replicates, number of samples, and number of individuals. Clin Chem 2012;58:1306-13.
7. Available online: https://www.eflm.eu/site/page/a/1148
8. Bartlett WA, Braga F, Carobene A, et al. A checklist for

critical appraisal of studies of biological variation. Clin Chem Lab Med 2015;53:879-85.
9. Carobene A, Marino I, Coşkun A, et al. The EuBIVAS Project: Within- and Between-Subject Biological Variation Data for Serum Creatinine Using Enzymatic and Alkaline Picrate Methods and Implications for Monitoring. Clin Chem 2017;63:1527-36.
10. de Maat MP, van Schie M, Kluft C, et al. Biological Variation of Hemostasis Variables in Thrombosis and Bleeding: Consequences for Performance Specifications. Clin Chem 2016;62:1639-46.

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