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Abstract

Background: Interpretation of the complete blood count (CBC) parameters requires reliable biological variation (BV) data. The aims of this study were to appraise the quality of publications reporting BV data for CBC parameters by applying the BV Data Critical Appraisal Checklist (BIVAC) and to deliver global BV estimates based on BIVAC compliant studies.

Methods: Relevant publications were identified by a systematic literature search and evaluated for their compliance with the 14 BIVAC criteria, scored as A, B, C or D, indicating decreasing compliance. Global CV_I and CV_G estimates with 95% CI were delivered by a meta-analysis approach using data from BIVAC compliant papers (grades A–C).

Results: In total, 32 studies were identified; four received a BIVAC grade A, 2 B, 20 C and 6 D. Meta-analysis derived CV_I and CV_G estimates were generally lower or in line with those published in a historical BV database available online. Except for reticulocytes, CV_I estimates of

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erythrocyte related parameters were below 3%, whereas platelet (except MPV and PDW) and leukocyte related parameters ranged from 5% to 15%.

Conclusions: A systematic review of CBC parameters has provided updated, global estimates of CV_I and CV_G that will be included in the newly published European Federation of Clinical Chemistry and Laboratory Medicine BV Database.

Keywords: biological variation; erythrocyte; haemoglobin; leukocyte; meta-analysis; platelets.

Introduction

The complete blood count (CBC) is one of the most commonly ordered blood tests in clinical practice. Defining analytical performance specifications (APSs) for each CBC component is essential to ensure that the measurement error will not distort the clinical interpretation of the result [1–4]. According to the consensus statement delivered by the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), the recommended approaches for deriving APS should preferably rely on (1) the effect of measurement performance on clinical outcome (model 1) or on (2) the biological variation (BV) of the measurand (model 2) [5, 6]. If APS based on these models cannot be made, state-of-the-art, defined as the highest level of performance technically achievable, could be used (model 3). However, it is generally agreed that analytical quality should be compared against objective APSs, considering that models 1 or 2 are preferred [7, 8]. On the basis of a preliminary list prepared by the EFLM Task and Finish Group on Allocation of Laboratory Tests to Different Models for Performance Specifications (TFG-DM), most CBC components are assigned to the BV model [9].

The availability of BV data also allows the derivation of other parameters, such as (i) the index of individuality (II) the evaluation of the utility of population reference intervals, (ii) the reference change value (RCV), i.e. the estimate of a significant change in a timed series of results of an individual and (iii) the number of specimens required to obtain an accurate estimate of the homeostatic set point of the analyte [3, 10, 11].

Since the 1970s, many papers on BV of CBC parameters have been published. The medians of the BV estimates delivered by most of these publications have for the last decades been available in the historical BV database (HBVD), which was updated every 2 years until 2014 [12, 13]. However, concerns about the quality and validity of these data have been raised [14, 15]. In response to this, the EFLM BV Working Group (EFLM BV-WG) and Task Group on the BV Database have developed the BV Data Critical Appraisal Checklist (BIVAC) [16], which is designed to assess the quality of BV publications by verifying whether all essential elements that may impact upon veracity and utility of the associated BV estimates are present. Furthermore, a meta-analysis approach to deliver global estimates based on BIVAC compliant studies has been constructed. For CBC parameters, obtaining reliable BV estimates is particularly challenging. Due to stability issues, blood samples cannot be stored and, consequently, the measurement of all samples from the same person cannot be performed in a single centre in a single analytical run on the same day, which is the usual recommended approach. Generally, to obtain reliable BV data of CBC parameters, the protocol and the checklist developed by EFLM BV-WG [17, 18] should be followed, as in two recently published national studies [19–22].

The aims of the present study were to systematically appraise published BV data of CBC parameters by use of the BIVAC [16] and to extract BV data from BIVAC-compliant studies to deliver global BV estimates for CBC parameters by meta-analysis.

Materials and methods

Bibliographic research

Firstly, the references in the HBVD [12] related to the BV of CBC parameters were considered. This retrieved 18 papers, all of which were published before 2014. Thereafter, a systematic bibliographic research was performed in Web of Science and PubMed in November 2018, applying the terms “biological variation”, “biological variability”, “CBC”, “haematology”, with limits ‘‘Title/Abstract, Human Subjects, English”. An additional 14 papers were identified by this approach, giving in total 32 papers that were included in the study. Studies published prior to 2014 are identified by the numbers they have had assigned in the HBVD. The same numbering system is used in the EFLM Biological Variation Database [23] for papers published after 2014 (Supplementary Table 1).

Appraisal of publications by the BIVAC

All 32 papers were evaluated by two reviewers independently for their compliance with the 14 BIVAC quality items (QIs), which may receive scores A, B, C and/or D [16]. In the BIVAC, an overall grade A indicates full compliance with all QIs; a grade B is given if the lowest QI

score achieved is a B, and similarly grade C, if the lowest QI score is C. Studies are graded D if they lack essential BIVAC elements (QI 2–4). A subscript system is applied to illustrate the scores. For example, if a paper was classified as "C" due to the items 2,5,6,7, the grade of the paper is given as "$C_{2,5,6,7}$".

The method used to evaluate the BV studies has recently been described in detail by Díaz-Garzón [24] and González-Lao et al. [25]. When estimates from different populations or sampling intervals were included for the same measurand, BIVAC assessment and data extraction were performed for each subgroup/sampling interval. In addition, data for 30 descriptive items such as study duration, subjects' health status, sample types, sampling time and interval, analytical methods, number of samples, etc. were extracted from each paper. Confidence intervals (CIs) at 95% for both CV_I and CV_G were calculated as described by Burdick and Graybill [26].

Meta-analysis

For each CBC parameter, global CV_I and CV_G were estimated by a meta-analysis approach using data extracted from BIVAC-compliant [16] papers, i.e. those receiving an overall BIVAC grade A, B or C. Papers classified as D and studies/study subgroups that did not fulfill the following inclusion criteria were excluded: (i) healthy individuals, (ii) subject age (min–max; 18–75 years) and (iii) estimates for within day variation [24].

Furthermore, studies/study subgroups were excluded from the meta-analysis if the following criteria were fulfilled:

- the CV_I and CV_G estimates were reported as 0; as was the case for platelets in paper 28
- results for more than one CBC component were reported as one parameter; monocyte, basophils and eosinophils as in paper 36
- more than one sample was collected from the same subjects at the same sampling time; paper 154
- CV_I and CV_G estimates were derived from only two samples per subjects; paper 291
- capillary samples; Hb and Hct from paper 9.

To calculate the weight of each estimate in the meta-analysis, the quality grade "A", "B" and "C" were given a factor of 4, 2 and 1, respectively, and multiplied with the inverse width of their CI [16, 25]. Estimates from subgroups (e.g. male and female) from the same study were combined prior to being included in the meta-analysis. Finally, a percentile boot strap technique was used to calculate the CI of the global estimate [25, 27].

Table 1: Number of papers (N), number of study subgroups (n) and the BIVAC grade for publications reporting BV estimates for CBC parameters.

CBC parameters	N	n	BIVAC grade			
			A	B	C	D[a]
Erythrocyte	12	33	2	1	9	4
Haemoglobin	21	60	2	1	18	6
Haematocrit	16	43	2	1	13	3
MCV	12	29	2	1	9	4
MCH	11	26	2	1	8	3
MCHC	11	28	2	1	8	4
RDW	4	8	2	0	2	1
Reticulocyte	5	10	2	1	2	0
Reticulocyte – He	2	6	2	0	0	0
Leukocyte	12	33	2	1	9	4
Lymphocyte	10	25	2	1	7	3
Monocyte	8	23	2	0	6	3
Neutrophil	9	25	2	1	6	3
Eosinophil	7	22	2	0	5	3
Basophils	7	21	2	0	5	3
Platelet	13	32	2	1	10	3
Plateletcrit	5	8	2	0	3	0
MPV	7	10	2	0	5	3
PDW	3	5	2	0	1	0
P-LCR	2	4	2	0	0	0

MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution wide; MPV, mean platelet volume; PDW, platelet distribution wide; P-LCR, platelet larger cell ratio; N, number of publications used to estimate the BV of CBC parameters; n, number of subgroups; [a]D papers and their subgroups were not included in N and n.

Results

Table 1 shows the number of papers, their BIVAC grade and the number of subgroups (different study populations, sampling intervals, etc.) included in our review. The number of publications per analyte is variable. For well-established parameters such as erythrocytes, Hb, leukocytes and platelets a number of papers ranging from a minimum of 12 for erythrocyte and leukocyte and a maximum of 21 for Hb were identified, whereas for reticulocyte haemoglobin equivalent (Ret-H_e) and platelet larger cell ratio (P-LCR) only two papers were identified.

The different publications were assigned the following BIVAC grades: A, n = 4; B, n = 2; and C, n = 20 (Supplementary Table 1). QIs related to the statistical approach such as inadequate outlier analysis and/or lack of variance homogeneity testing were the most frequent cause (19/26; 73%) of the BIVAC C grade classification (Table 1). In addition, six publications were classified as D, mainly due to sampling problems such as irregular timing of sample collections (BIVAC QI-3) [16]. The study designs described

Table 2: Meta-analysis derived within-subject (CV_I) and between-subject (CV_G) BV estimates with 95% CIs of CBC parameters and estimates from the HBVD.

Measurands	Meta-analysis-based estimates								HBVD	
	N_I	n_I	Mean ± SD	CV_I (CI), %	N_G	n_G	Mean ± SD	CV_G (CI), %	CV_I, %	CV_G, %
Erythrocyte, $\times10^{12}$/L	7	12	4.82 ± 0.33	2.80 (1.96–3.07)	5	10	4.85 ± 0.36	6.29 (6.16–7.40)	3.20	6.30
Haemoglobin, mmol/L	11	21	8.77 ± 0.61	2.71 (1.72–2.80)	6	13	8.72 ± 0.63	6.07 (3.20–6.28)	2.85	6.80
Haematocrit, L/L	6	13	0.43 ± 0.03	2.71 (2.24–3.40)	6	13	0.43 ± 0.03	5.45 (3.40–5.51)	2.70	6.41
MCV, fL	7	12	88.4 ± 2.37	0.75 (0.64–1.17)	6	11	88.0 ± 2.10	3.78 (3.40–4.68)	1.40	4.85
MCH, fmol	6	9	1.85 ± 0.05	0.85 (0.24–1.60)	5	8	1.84 ± 0.05	4.30 (4.06–5.31)	1.40	5.20
MCHC, mmol/L	6	11	20.8 ± 0.38	0.95 (0.60–1.10)	5	10	20.9 ± 0.38	1.49 (1.25–2.30)	1.06	1.20
RDW, fL	3	7	40.9 ± 1.36	1.51 (1.08–1.90)	2	6	40.5 ± 0.96	4.75 (3.67–7.26)	3.5	5.70
Reticulocyte, $\times10^{12}$/L	3	8	0.056 ± 0.009	9.74 (6.44–11.0)	3	8	0.056 ± 0.009	27.11 (22.13–30.53)	11	29
Reticulocyte – He, pg	2	6	33.4 ± 0.59	1.92 (0.75–3.40)	2	6	33.4 ± 0.59	3.38 (2.72–4.11)	NA	NA
Leukocyte, $\times10^9$	7	12	6.62 ± 0.39	10.01 (8.90–11.35)	4	7	6.75 ± 0.47	16.48 (15.78–23.70)	11.40	21.30
Lymphocyte, $\times10^9$	5	7	2.12 ± 0.08	10.13 (9.45–13.59)	4	6	2.12 ± 0.09	23.87 (21.30–25.10)	10.20	35.30
Monocyte, $\times10^9$	3	5	0.49 ± 0.11	12.85 (11.79–16.40)	2	4	0.54 ± 0.04	18.30 (15.86–22.26)	17.80	49.8
Neutrophil, $\times10^9$	5	8	3.81 ± 0.36	13.61 (6.30–20.37)	3	5	3.79 ± 0.48	21.16 (20.70–32.60)	17.10	32.80
Eosinophils, $\times10^9$	3	5	0.11 ± 0.06	14.38 (12.52–20.8)	2	4	0.13 ± 0.02	64.25 (59.89–70.50)	21.0	76.4
Basophils, $\times10^9$	3	4	0.05 ± 0.01	11.34 (11.21–32.0)	2	3	0.04 ± 0.002	25.07 (22.1–29.9)	28.0	54.8
Platelet, $\times10^9$	6	10	232.2 ± 15.6	7.1 (4.49–7.69)	5	8	232.3 ± 19.1	16.17 (10.80–22.36)	9.10	21.90
Plateletcrit, %	3	5	0.25 ± 0.02	5.94 (4.97–11.6)	2	4	0.26 ± 0.01	13.33 (12.49–14.08)	11.90	NA
MPV, fL	4	6	10.2 ± 0.84	2.02 (1.55–4.30)	2	4	10.6 ± 0.33	6.96 (6.96–8.10)	4.30	8.10
PDW, fL	2	4	12.61 ± 0.65	3.43 (3.10–3.69)	2	4	12.61 ± 0.65	12.31 (11.95–12.79)	2.80	NA
P-LCR, %	2	4	29.7 ± 2.60	5.70 (4.78–6.60)	2	4	29.7 ± 2.60	20.42 (19.79–21.27)	NA	NA

HBVD, Historical Biological Variation Database; CI, confidence intervals; N_I, number of papers used in meta-analysis of CV_I; N_G, number of papers used in meta-analysis of CV_G; n_I, number of subgroups used in meta-analysis of CV_I; n_G, number of subgroups used in meta-analysis of CV_G; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution wide; MPV, mean platelet volume; PDW, platelet distribution wide; P-LCR, platelet larger cell ratio.

in the 26 eligible papers showed marked heterogeneity, reporting BV results for different subgroups of subjects, such as sex, age (adults (between 18 and 75 years), elderly (>75 years), sampling intervals (hourly, daily, weekly, monthly). We critically appraised data and assigned a BIVAC grade for each of these subgroups, obtaining in total 73 subgroup data sets (Supplementary Table 1), but except for two papers (papers 36 and 291) there was no difference between the BIVAC grade assigned to different subgroup data sets derived from the same study. The meta-analysis derived results from our study were generally in line with or lower than those presented in the HBVD (Table 2). Estimates of CV_I and CV_G with 95% CI for the CBC parameters from all reviewed studies are shown in Figure 1 (erythrocytes, leukocytes and platelets) and Supplementary Figures 1–37, and the reasons for exclusion from meta-analysis are detailed. Supplementary Table 2 shows the scoring system in detail for erythrocytes.

Discussion

To the best of our knowledge, this is the first study to perform a systematic review of the literature of BV of CBC parameters and to critically appraise these papers. The majority of the reviewed publications obtained a BIVAC C or D grade (Table 1). To obtain reliable estimates of BV from meta-analysis, it is important that included data are derived from studies with similar study populations and study designs. Therefore, in addition to BIVAC criteria, we applied additional exclusion criteria which caused five publications to be excluded from the meta-analysis.

Except for reticulocytes, CV_I estimates of erythrocyte related parameters were below 3%, whereas platelet (except MPV and PDW) and leukocyte related parameters ranged from 5% to 15% (Table 2). The CV_I estimates derived for MCV, MCH and MCHC were extremely low and with current technologies it is not easy to use and adopt APSs based on these results if the APSs are set at the desirable level, which is the most common approach. It may therefore be necessary to consider alternative approaches such as minimum level [3, 10], outcome studies (model 1) or state of the art (model 3) [6] to set APSs.

The HBVD has presented as the estimates of medians of data from publications published until 2014 [12]. There are no measures of uncertainty included in this overview and thus, direct statistical comparison with the results of our study is therefore not possible. We, however,

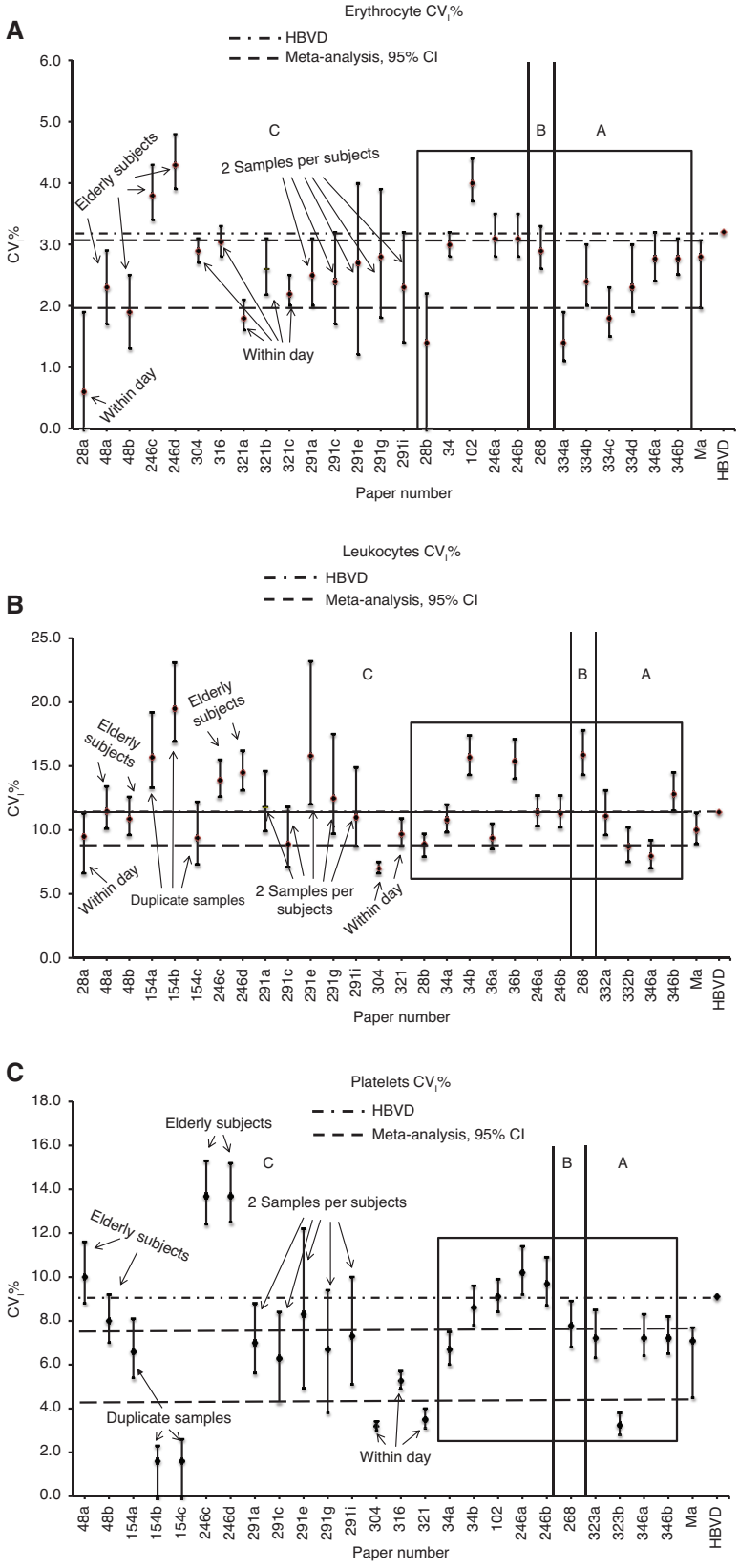

Figure 1: The CV_I estimates with 95% confidence intervals for (A) erythrocytes, (B) leukocytes and (C) platelets.
The boxes indicate which studies were included in the meta-analysis, as well as the BIVAC grades awarded to the different studies. Reasons for exclusion from the meta-analysis are also shown. The different papers are identified on the x-axis with the letters indicating different study subgroups (see Supplementary Table 1).

evaluated whether the CV_I and CV_G estimates included in the HBVD were within the limits of CIs for the estimates obtained from meta-analysis; this was the case for the CV_I of eight out of 18 analytes and the CV_G of seven out of 16 analytes (Table 2). For the remainder, the point estimates for both CV_I (except PDW) and CV_G (except MCHC) in the HBVD were higher than the upper limits of CIs calculated from meta-analysis. It is worth noting that a number of the same studies makes up the basis for both the estimates presented in the HBVD as well as in our study. The lower CV_I and CV_G estimates derived from meta-analysis are probably caused by a lower weight given to results from studies considered to be of inferior methodological quality.

The CV_I estimates for erythrocyte related parameters were much lower than those derived for leukocyte and platelet parameters (Table 2). This is probably caused by the longer turnover period of erythrocyte (≈4 months) [28] related parameters and that erythrocytes are not "consumed" in the same way as platelets (7–10 days) [29] and leukocytes [30]. The lifespan of leukocyte subgroups in circulation varies and ranges from days (neutrophils) to years (memory cells). Except some subset of lymphocytes [31, 32], leukocytes have rapid turnover in the circulation.

For the meta-analysis, we excluded within-day studies because the diurnal variation for many constituents can be high and diurnal variation may be used for different purposes than the CV_I calculated from studies with longer sampling intervals. Despite some exceptions, however, based on four studies (papers 28a, 304, 316, 321) the within day CV_I and CV_G were not significantly different from daily, weekly or monthly variations provided by other studies (Supplementary Table 1). Three studies assigned a BIVAC grade A (number 323, 332 and 334) reported the CV_I and CV_G of CBC parameters based on (i) weekly samplings for 35 days (medium-term) and (ii) daily sampling for 5 days (short-term). The short-term CV_I were significantly lower than those based on weekly samplings for MCV (females), RDW (females), reticulocytes (males) and Ret-H_e (male). Additionally, the short term CV_I of platelet groups parameters were significantly lower than the medium-term CV_I, whereas no significant differences were observed for the other parameters.

One paper (paper 28) reported a higher CV_I estimate for basophil based on monthly samplings for 6 months, than the papers based on daily or weekly sampling intervals and shorter study periods (Supplementary Table 1). However, variations in study design were observed, and in order to clarify the effect of different sampling intervals and study duration on BV of CBC parameters, standardised studies are warranted.

In the meta-analysis, we only included studies performed in adults between the age of 18 and 75. Despite the inclusion of different age groups in various studies, the influence of age on BV has not been studied in detail. We found that the CIs we derived based on results for Hb in paper 325 were extremely high in comparison to those found in other studies (Supplementary Figure 2). This may be related to the study design or to the included study population. Additionally, the CV_I estimates of platelets derived from one study on subjects aged 80–92 years old (paper 246 c,d) were higher than estimates from healthy adults. Carobene et al. assessed the influence of age on BV estimates for creatinine, urate, calcium, albumin, total cholesterol, high density lipoprotein and low-density lipoprotein-cholesterol, triglycerides and iron. Except for albumin, they found significantly lower CV_I estimates in subjects above the age of 78 compared to those below 36 years [33].

Theoretically, study-related factors such as sex, design and pre-analytical handling might affect the derived BV of CBC parameters. The mean concentration of erythrocytes and Hb in women is lower than men. Although we are interested in variation and not the mean level, the menstrual cycle of women may influence the BV of erythrocytes and Hb, but there is no data to support this.

Special attention should be given to CBC parameters whose normal levels are close to their limit of quantitation (LOQ), such as basophils and eosinophils. The uncertainty of methods around LOQ is higher than the normal concentration. Increasing uncertainty makes methods less sensitive and gives a higher CV_A which causes wider CI of both CV_I and CV_G. At low concentration particularly around LOQ the CV_A is higher and therefore it may be better to report BV data in SD instead of CV. Although the CV_I and CV_G estimates of both eosinophils and basophils obtained from our meta-analysis were lower than the CV_I and CV_G in the HBVD, the estimated BV of these two tests were higher than most of the other CBC parameters probably due to the low concentration of these cells (Table 2).

Conclusions

A systematic review identified more than 30 papers delivering BV data for CBC components, but only four of these studies were assigned a BIVAC grade A [19–22] and the majority a C or D grade. In our study, meta-analysis of BIVAC compliant studies (grade A, B and C) has enabled publication of updated, global estimates of CV_I and CV_G for CBC parameters. These BV estimates will along with

estimates for other study populations and other measurands be included in the EFLM Biological Variation Database [23]. The CBC parameters make up a large group of heterogeneous tests and with continuous technological developments, new parameters will be added. The BV data of parameters such as Ret-H_e and P-LCR are limited and new studies should be encouraged to cover these parameters. In general, we encourage more high-quality studies to be performed for CBC parameters.

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