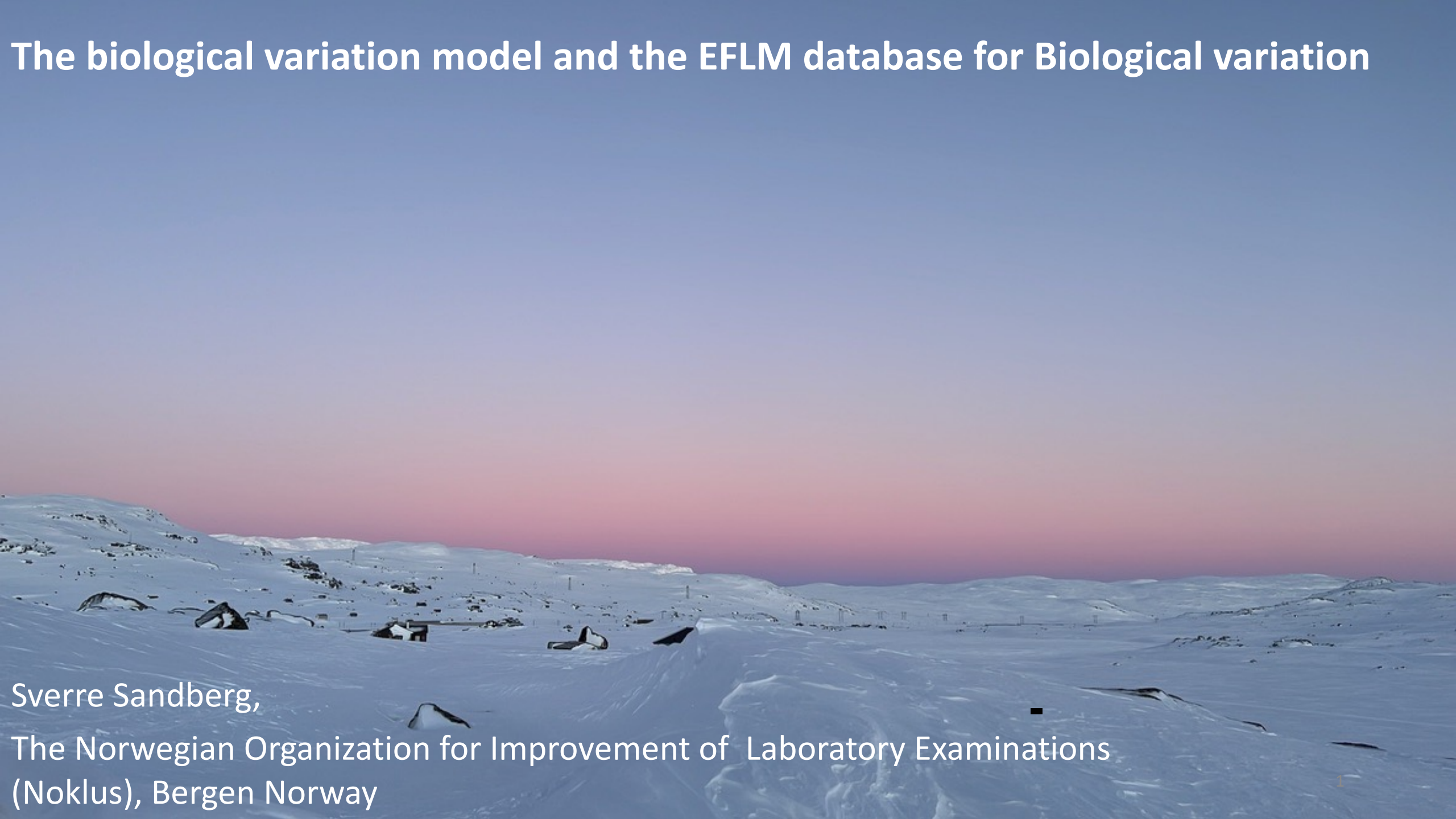
The biological variation model and the EFLM database for Biological variation



Sverre Sandberg,

The Norwegian Organization for Improvement of Laboratory Examinations (Noklus), Bergen Norway

What I will talk about

- The biological variation database – how reliable data can be established

- What is Analytical performance specification based on BV? Are they based on «biological variation»?

- A new concept for calculating minimum, desireable and optimum APS

EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

European Commission
Joint Research Centre
IRMM
Institute for Reference Materials and Measurements

CIRME
Università degli Studi di Milano

1st EFLM Strategic Conference

Defining analytical performance goals 15 years after the Stockholm Conference

8th CIRME International Scientific Meeting

Milan (IT)
24-25 November 2014

with the auspices of ifcc International Federation of Clinical Chemistry and Laboratory Medicine

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REGISTRATION FEE
EUR 305,00 (VAT 22% included)

The registration fee includes:
- Coffee break & lunch buffet as indicated in the programme
- Certificate of participation

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The official language of the conference is English.

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What is analytical performance specifications?

DE GRUYTER Clin Chem Lab Med 2015; 53(6): 833–835

Consensus Statement

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

Models to set Analytical Performance Specifications – what quality should we have?

Model 1. Based on the effect of analytical performance on clinical outcomes

1a. Direct outcome studies

1b. Indirect outcome studies

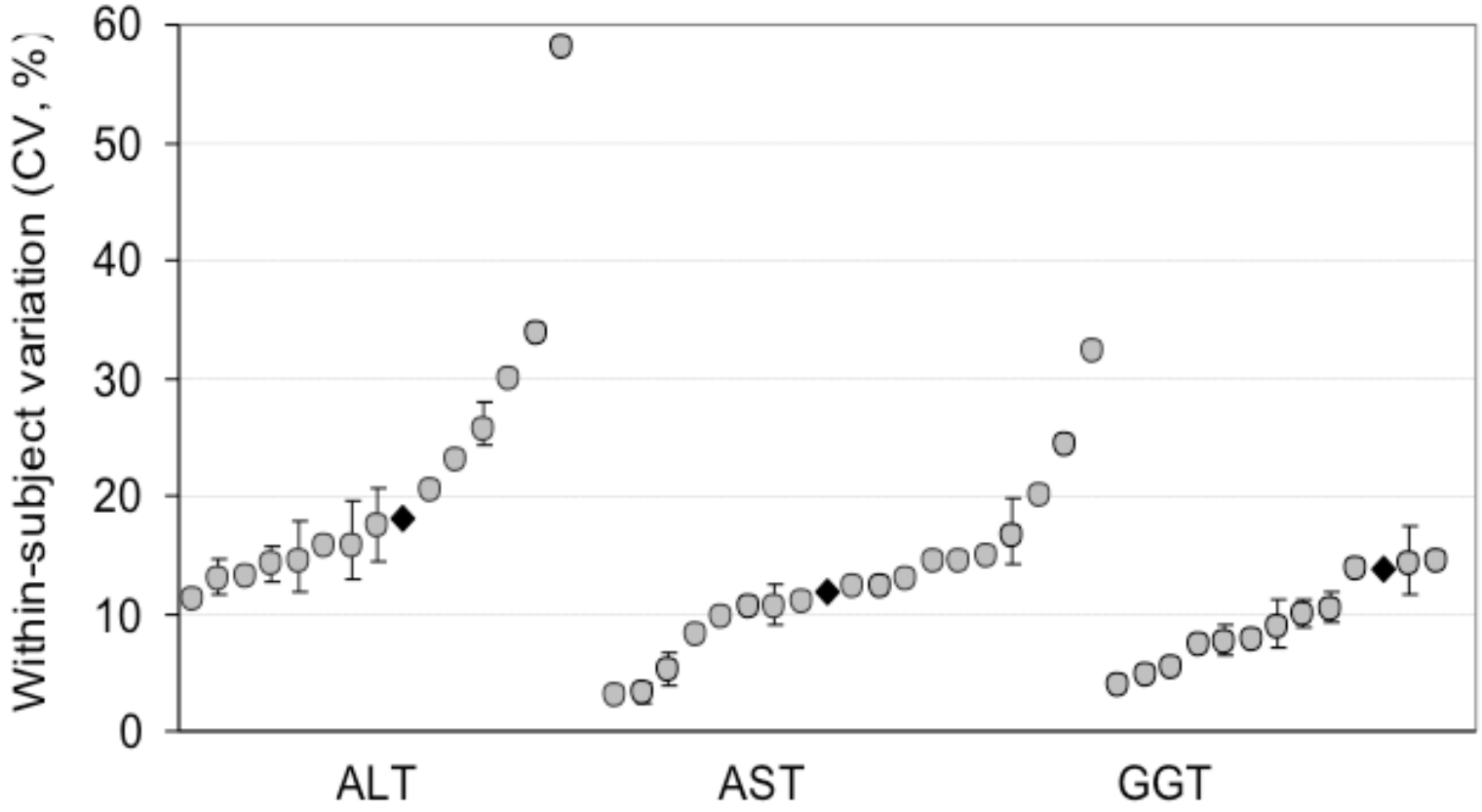
Model 2. Based on components of biological variation of the measurand

(- to minimise analytical noise to biological variation)

Model 3. Based on state of the art

Within-subject variation – **is the data reliable?**

Data from the Rico/Westgard database



Carobene A et al Clin Chem Lab Med. 2013;51:1997–2007.

Model 2. Based on components of biological variation of the measurand

This attempts to minimize the ratio of ‘analytical noise’ to the biological signal. The advantage is that it can be applied to most measurands for which population-based or subject-specific biological variation data can be established.

There are limitations to this approach, including the need to carefully assess the relevance and validity of the biological variation data, e.g., the presence of ‘steady state’, the appropriate time intervals, effect of inter-current illness and effect of measurand concentrations.


SEQC

Clinical Chemistry 64:3
501–514 (2018)

The Biological Variation Data Critical Appraisal Checklist: A Standard for Evaluating Studies on Biological Variation

Aasne K. Aarsand,[1,2*] Thomas Røraas,[2] Pilar Fernandez-Calle,[3,4] Carmen Ricos,[4] Jorge Díaz-Garzón,[3,4] Niels Jonker,[5] Carmen Perich,[4,6] Elisabet González-Lao,[4,7] Anna Carobene,[8] Joana Minchinela,[4,9] Abdurrahman Coşkun,[10] Margarita Simón,[4,11] Virtudes Álvarez,[4] William A. Bartlett,[12] Pilar Fernández-Fernández,[4] Beatriz Boned,[4,13] Federica Braga,[14] Zoraida Corte,[4,15] Berna Aslan,[16] and Sverre Sandberg[1,2,17] on behalf of the European Federation of Clinical Chemistry and Laboratory Medicine Working Group on Biological Variation and Task and Finish Group for the Biological Variation Database

BACKGROUND: Concern has been raised about the quality of available biological variation (BV) estimates and the effect of their application in clinical practice. A European Federation of Clinical Chemistry and Laboratory Medicine Task and Finish Group has addressed this issue. The

D scores. Outlier analysis and variance homogeneity testing were scored as C in >60% of 847 cases. Metaanalysis delivered a CV_I estimate for ALT of 15.4%.

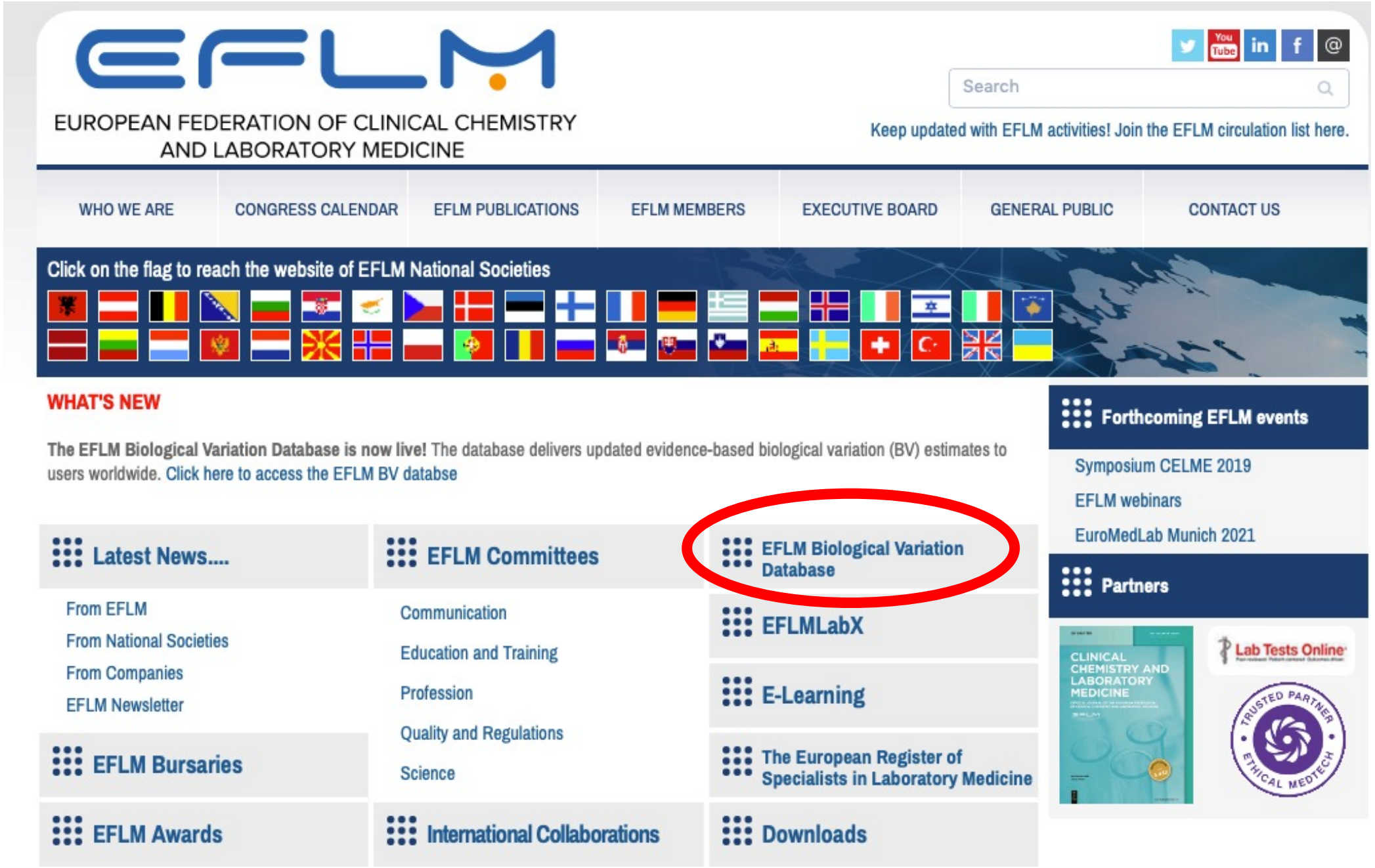
CONCLUSIONS: Application of BIVAC to BV publica

Critical appraisal check list

- ✓Papers are categorized as A, B, C and D depending on their methodological quality
- ✓The checklist contains 14 items, and
- ✓22 items are extracted from each paper and presented in the EFLM BV database.
- ✓A huge efforts has been performed to categorize the existing literature on BV

Meta-analysis, weighting the average of the CV_I of eligible studies

- Weight according to quality category, A, B, C
- Weight according to number of samples/subjects (confidence intervals)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The EFLM Biological Variation Database is now live! The database delivers updated evidence-based biological variation (BV) estimates to users worldwide. Click here to access the EFLM BV databse
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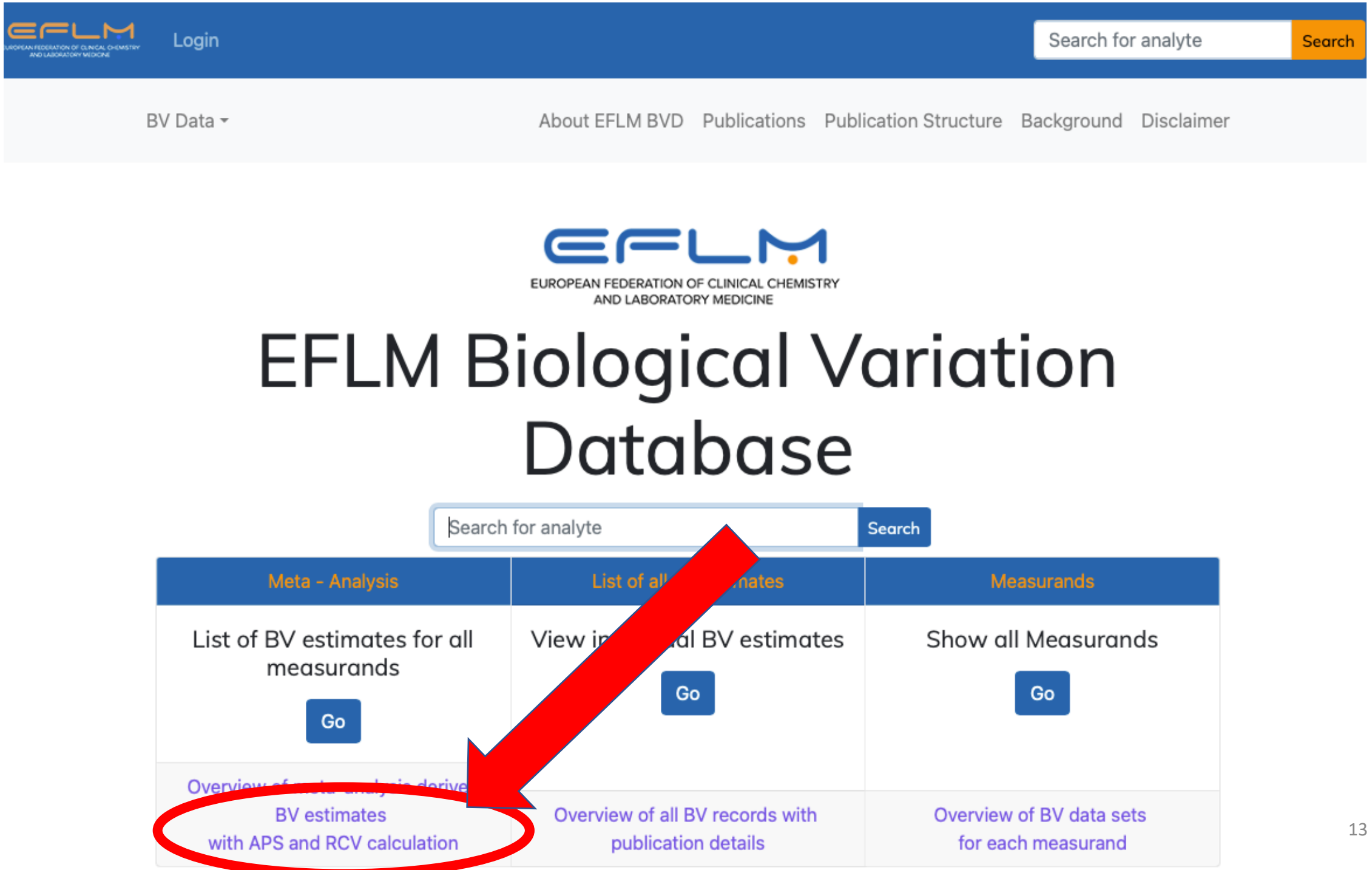
The Biological Variation Database was launched during Euromedlab in Barcelona in 2019 and has been much improved since then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Overview of all BV records with publication details
Overview of BV data sets for each measurand

Newer approaches to estimate biological variation

Papers in Press. Published January 28, 2019 as doi:10.1373/clinchem.2018.290841
The latest version is at http://clinchem.aaccjnls.org/cgi/doi/10.1373/clinchem.2018.290841

Clinical Chemistry 65:4
000–000 (2019)

General Clinical Chemistry

Estimates of Within-Subject Biological Variation Derived from Pathology Databases: An Approach to Allow Assessment of the Effects of Age, Sex, Time Between Sample Collections, and Analyte Concentration on Reference Change Values

Graham Ross Dallas Jones[1,2*]

Papers in Press. Published July 1, 2019 as doi:10.1373/clinchem.2018.300145
The latest version is at http://clinchem.aaccjnls.org/cgi/doi/10.1373/clinchem.2018.300145

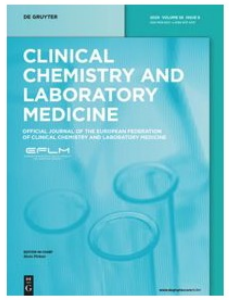
Clinical Chemistry 65:8
995–1005 (2019)

A Bayesian Approach to Biological Variation Analysis

Thomas Røraas,[1*] Sverre Sandberg,[1,2,3] Aasne K. Aarsand,[3] and Bård Støve[4]

BACKGROUND: Biological variation (BV) data have many applications for diagnosing and monitoring disease. The standard statistical approaches for estimating BV are sensitive to "noisy data" and assume homogeneity of within-participant CV. Prior knowledge about BV is mostly ignored. The aims of this study were to develop Bayesian models to calculate BV that (*a*) are robust to "noisy data," (*b*) allow heterogeneity in the within-participant CVs,

Biological variation (BV)[5] data, describing the natural variation observed for most constituents in the human body, have many applications for diagnosing and monitoring disease *(1)*. The magnitude of within-participant BV (CV_I) describes the expected variation of an analyte around a homeostatic set point within an individual and the between-participant BV (CV_G) variation between these set points *(2)*. For the BV estimates to be clinically



Published by De Gruyter

Volume 60 Issue 4 - Special Issue: Biological va… the 1st Strate… Issue Editors: … Carobene an…

Issue of Clinical Che… (CCLM)

DE GRUYTER

Clin Chem Lab Med 2023; 61(5): 741–750

Review

Sverre Sandberg*, Anna Carobene, Bill Bartlett, Abdurrahman Coskun, Pilar Fernandez-Calle, Niels Jonker, Jorge Díaz-Garzón and Aasne K. Aarsand

Biological variation: recent development and future challenges

https://doi.org/10.1515/cclm-2022-1255
Received December 10, 2022; accepted December 12, 2022; published online December 20, 2022

Abstract: 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 different study designs, both by experimental studies and studies utilizing previously analysed routine results derived from laboratory databases. The different BV applications include using … other standards for deriving and reporting BV data, the EFLM Biological Variation Database and new applications of BV data including personalized reference intervals and measurement uncertainty.

Keywords: biological variation; BIVAC; EuBIVAS; personalized reference intervals (prRI); reference change value.

Background

DE GRUYTER

Editorial

Sverre Sandberg*, Anna Carobene and Aasne K. Aarsand

Biological variation – eight yea… Strategic Conference of EFLM

https://doi.org/10.1515/cclm-2022-0086

Keywords: analytical performance specifications (APS); biological variation (BV); Biological Variation Data Critical Appraisal Checklist (BIVAC); European Biological Variation Study (EuBIVAS); index of individuality (II); reference change value (RCV).

to set APS: th… second on B… conjunction … nized that mu… with uncertai… need for critic… new studies

Search Results

Cholesterol

Cholesterol

Analytical Performance Specification | RCV Calculation

Matrix	BV Estimate	median CV estimate	lower CI limit	higher CI limit	Comments	Date Updated
Serum/plasma		5.3	5.1	6.3		27/3/2023
Serum/plasma		16.7	14.8	17.4		27/3/2023

Colour Key for References

Included In Meta Analysis | Not Included In Meta Analysis

Reference	Dataset	Estimate of CVI	Estimate of CVG	Gender	Age	State of Well Being	Matrix	Sampling Interval
Intra-individual variation of some analytes in								

Personal View *Ann Clin Biochem* 1997; **34**: 8–12

Proposals for setting generally applicable quality goals solely based on biology

Callum G Fraser, Per Hyltoft Peters
From the Directorate of Biochemical Medicin
DD1 9SY, UK, [1]*Clinical Chemistry Departm*
[2]*Clinical Biology Department, Institute of Hy*
[3]*Clinical Biochemistry Department, Universit*

The current trend towards introduction of tc
quality management in laboratory medic
means that objective quality goals must
clearly defined *a priori*.[1] Objective selection a
evaluation of analytical systems require t
quality goals are available for preparati
specifications, appraisal of options
tion of experimental data[2] and
internal quality control p
instituted only if the quality

Scand J C b Invest 1988; 48: 757–764

Analytical goals fo ce of common
reference int ratories throughout
a geog

NS,*† P. HYLTOFT PETERSEN,† O. BLAABJERG†
ER†
tment of Biochemical Medicine, Ninewells Hospital and Medical School, Dundee, Scotland,
and †Department of Clinical Chemistry, Odense University Hospital, Odense C, Denmark

Should they be revised?

Models to set Analytical Performance Specifications

Model 1. Based on the effect of analytical performance on clinical outcomes

1a. Direct outcome studies

1b. Indirect outcome studies

Model 2. Based on components of biological variation of the measurand

(- to minimise analytical noise to biological variation)

Model 3. Based on state of the art

Imprecision

Imprecision: $CV_A < 0.5 \times CV_I$

The factor 0.5 refers to desirable APS and indicates that imprecision accounts for 12% of the total variation

Bias

Is the “BIAS formula” based on biological variation???
(minimising analytical noise to biological variability)

Bias: $< 0.25 \times (CV_I^2 + CV_G^2)^{1/2}$

Scand J Clin Lab Invest 1988; 48: 757–764

Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area

E. M. S. GOWANS,*† P. HYLTOFT PETERSEN,† O. BLAABJERG† & M. HØRDER†

*Department of Biochemical Medicine, Ninewells Hospital and Medical School, Dundee, Scotland, and †Department of Clinical Chemistry, Odense University Hospital, Odense C, Denmark

From the paper:

«We propose that the bias should not exceed $0.25 \times (CV_I^2 + CV_G^2)^{1/2}$ when analytical imprecision is almost nothing,

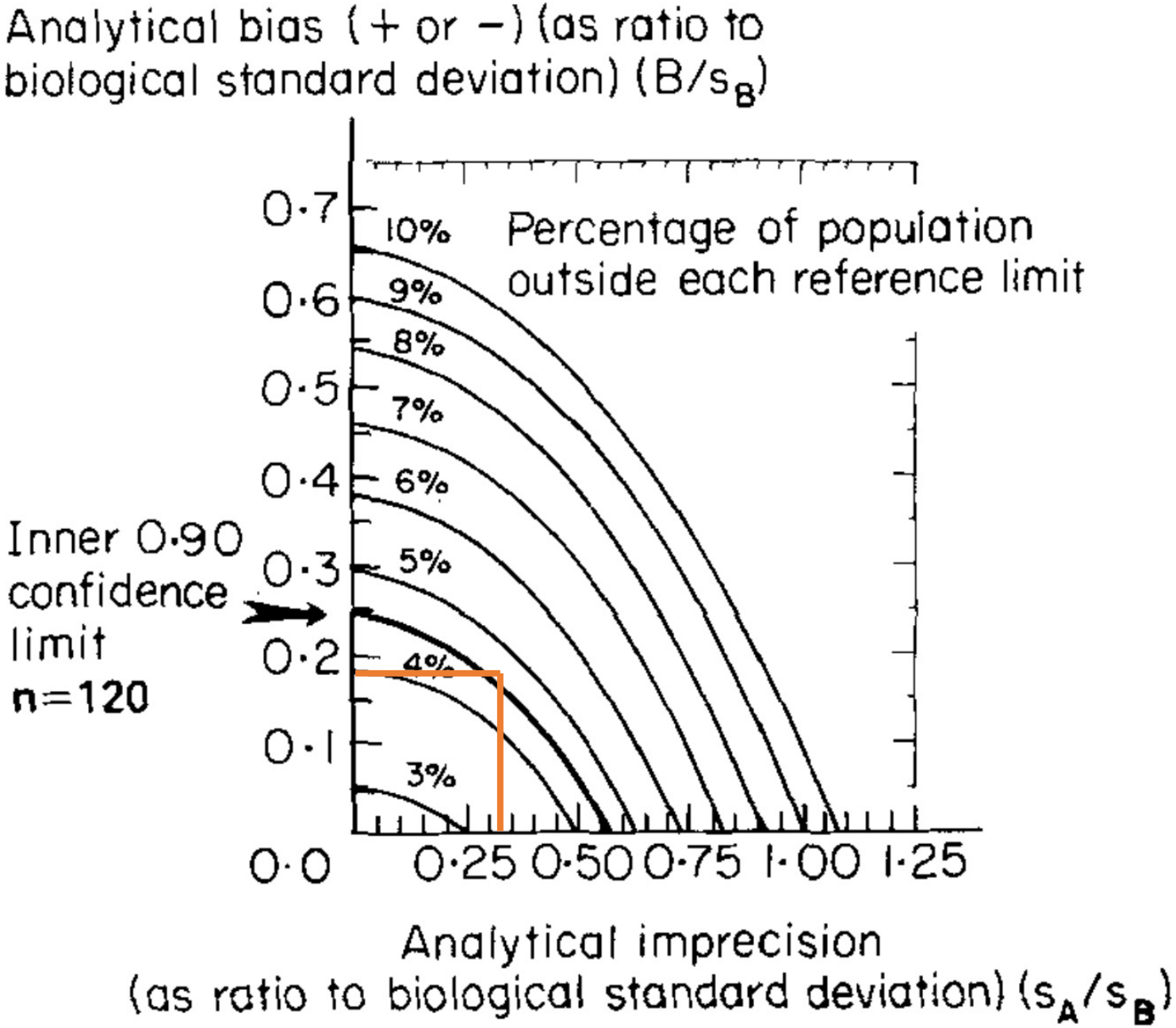
or that the percentage of the population outside each reference limit should not exceed 4.4% for a combination of analytical imprecision and bias»

Bias

The basis for this recommendation was that, *when the 120 population sample size recommended by the International Federation of Clinical Chemistry was selected,* then this was the maximum bias allowable to achieve the maximum acceptable percentage of the population outside each limit for the 0·90 confidence interval of each of the reference limits, namely 4·4%.

The "bias" APS is a combination of BV and type 1b outcome study (simulation)

It assumes that imprecision = 0



For example, for glucose, if the imprecision is 2.5% (desireable) the "bias formula" will be:

Bias: $< 0.18 \times (CV_I^2 + CV_G^2)^{1/2}$

So we should be careful when using the «bias formula»

1. Orginally it was used for sharing reference intervals
2. It assumed that ref intervals were based on 120 persons
3. It assumed gaussian distribution
4. It assumed that imprecision = 0
5. It then has the same limitation as the total error formula since the labs never have imprecision= 0
6. (- and it is not based on biological variation)

Total allowable error (TAE)

- The formula that considers both bias and imprecision was developed for EQA organizers and has been widely applied since it is easy to use.

- $TAE < 1.65 \times (0.5 \times CV_I) + 0.25 \times (CV_I^2 + CV_G^2)^{1/2}$

- However, this model for deriving total allowable error from biological variation data is flawed. It sums up two mutually exclusive terms, i.e., maximum allowable bias and maximum allowable imprecision, resulting in an overestimating allowable total error. For these reasons, this approach should be applied with caution.
- - and it is based on a combination of a biological variation and type 1b study

Conclusions

- Information about the point estimates of the within- and between biological variation is greatly improved in the new EFLM BV-database.
- The essential concept of model 2 is that analytical noise should be low compared to biological variation
- The «bias formula» is actually (mainly) based on a Type 1b model


Thank you!!