

Rationale for using data on biological variation

Dr. Carmen Ricós
**Spanish Society of Clinical Biochemistry
and Molecular Pathology.**
Analytical Quality Commission



1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Rationale for using data on biological variation

QUESTION

Why data on biological variation (BV) are useful for assuring the laboratory role in healthcare and patient safety?

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Rationale for using data on biological variation

ANSWERS

1. BV data from healthy people
Applications and limitations.
2. BV data from patients.
What do we know up today?
Practical use

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people

BV COMPONENTS

- Within-subject (CV_I):
Random fluctuation around the homeostatic set point
- Between-subject (CV_G):
Differences of homeostatic set point between individuals

Simundic A et al. Clin Chem 2014; DOI:10.1373

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people

BV DATABASE

- CV_I has been determined for 358 analytes
- CV_I seems to be independent of:
 - age*, sex
 - number of subjects, number of samples per subject, time span*
 - geographical area, analytical procedure used

Minchinela J et al. <http://www.westgard.com/biodatabase-2014-update.htm>

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Example: s- Glucose (extract)

CV_I	CV_G	CV_A	N (sex)	T_{days}	Population (H)	Year
3,7	8,8	2,3	56 (M)	28	Young people	2013
4,2	11	2,4	40	28	Adults	1994
4,5	7,5	2,3	62 (F)	28	Young people	2013
...
5,6	8,2	2,3	78 (M)	28	Elderly	2013
6,8	7,3	2,3	64 (F)	28	Elderly	2013
...
11,4	9,1	1,2	30	8h	Children	2014
13,1	3,2	3,0	10	5	Adults	1983

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Example: s- Glucose (extract)

CV_I	CV_G	CV_A	N	T_{days}	S_s	Mean	Year
4,2	11	2,4	40	28	3	5.5	1994
...
4,7	6,1	2,1	14	70	10	5,3	1988
4,7	5,4	2,4	27	140	10	5,2	1989
5,0	7,7	3,4	20	365	12	5,2	1989
...
6,5	8,7	2,2	1105	60	9	4,8	1978
...
13,1	3,2	3,0	10	5	5	4,8	1993

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Example: s- Glucose (extract)

CV_I	CV_G	CV_A	City	Instrumentation	Year
4,7	5,4	2,4	Dundee	SMAC	1989
5,4	5,6	1,4	Stavanger	Glucu-Quant	2011
5,5	7,8	2,5	Bethesda	---	1970
5,5	8,2	2,3	Toledo	Cobas 6000	2013
6,5	8,7	2,2	San Francisco	Abott bicromatic	1978
8,0	14	18	Barcelona	Hitachi 747	1986
11,4	9,1	1,2	Toronto	Vitros 5,1	2014
13,2	--	1,5	Heerlen	Automatic analyzer	1985

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Exceptions: Time span within a day

Cholesterol		Troponin I	
CV _I	T _{hours}	CV _I	T _{hours}
1.5	8	3.4	4
2.4	8	6.1	4
3.4	0.5	9.7	4-6
...
6,1	Median CV _I	12,9	Median CV _I

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Exceptions: adults ≠ children

Analyte	Adults		Children	
	CV _I	CV _G	CV _I	CV _G
Ceruloplasmin	5.8	11	11 ↑	20
Glucose	5.6	7.5	11 ↑	9,1
GGT	13	42	2,7 ↓	19
CRP	42	76	19 ↓	125

Bailey D. Clin Chem 2014;60:518-529.

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

LABORATORY ROLE

- To help clinicians in diagnosis, prognosis and patients monitoring purposes



Analytical errors should be maintained
within allowable limits

1. Biological variation from healthy people Applications and limitations

LABORATORY ROLE

- Data on biological variation can be used to derive allowable limits for analytical imprecision, bias and total error:

QUALITY SPECIFICATIONS

Keny D et al. Scan J Clin Lab Invest 1999;59:585 (Stockholm consensus).
Cooper G et al. Clin Chem Lab Med 2012; 49:793-802 (Stockholm 10 years later)

1. Biological variation from healthy people Applications and limitations

- ✓ ANALYTICAL QUALITY SPECIFICATIONS
- For **monitoring** purposes analytical **imprecision** has to be limited.



If imprecision is maintained below $1/2 CV_I$, the contribution of lab error to the total variation is calculated as 12%.

Cotlove E. Clin Chem 1970;16:1028-32.

1. Biological variation from healthy people Applications and limitations

- ✓ ANALYTICAL QUALITY SPECIFICATIONS
- For **diagnosis, case finding and screening** purposes, **bias** has to be limited



If analytical bias is maintained below $1/4 (CV_I^2 + CV_G^2)^{1/2}$, population-based reference intervals can be shared.

Gowans EMS. Scan J Clin Lab Invest 1988;48:757-64

1. Biological variation from healthy people Applications and limitations

✓ INTERNAL QC

1. Define total allowable error (TA_E) Quality specification
2. Measure analytical imprecision (CV_A) and bias (B_A)
3. Calculate $\sigma = (TA_E - B_A)/CV_A$
4. Search for an operative rule

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

✓ INTERNAL QC

	CV_A	B_A	TA_E	σ
Amylase	1.6	-1.2	15	8.6
Cholesterol	1.6	2.3	8.5	3.9
Creatinine	2.2	4.3	8.9	2.1

Based on BV

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

✓ INTERNAL QC

	CV_A	B_A	TA_E	σ
Amylase	1.6	-1.2	15	8.6
Cholesterol	1.6	2.3	8.5	3.9
Creatinine	2.2	4.3	20	7.1

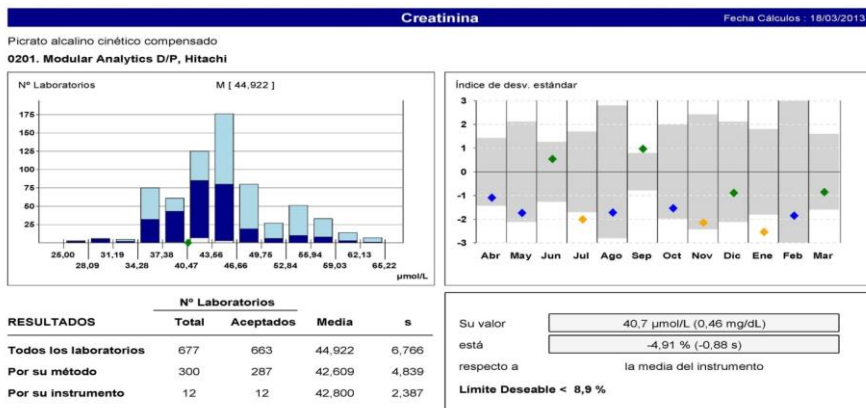
Based on
State of art

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

✓ EQA



1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014

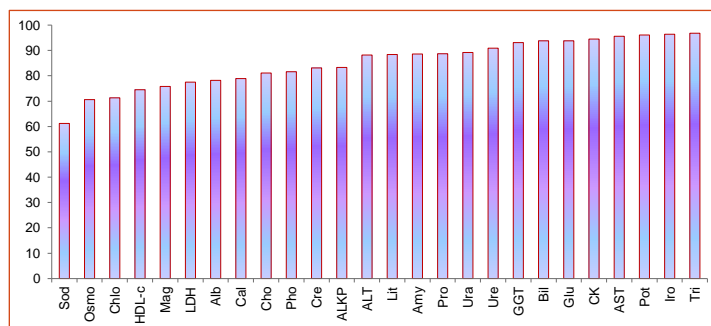


1. Biological variation from healthy people Applications and limitations

✓ EQA

% Results satisfying TA_E (based on BV)

SEQC 2013, 888 participants



1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014

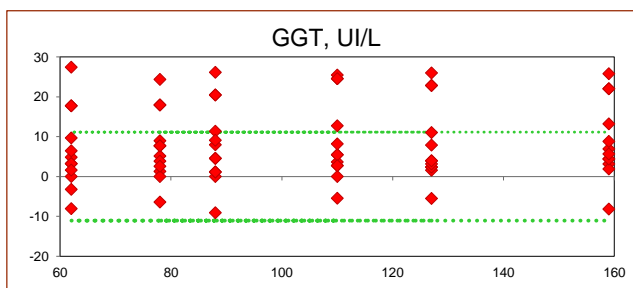


1. Biological variation from healthy people Applications and limitations

✓ EQA

% deviation to reference-method value (SKML 1st pilot)

10 Spanish participants



Perich C et al. Clin Chim Acta 2014;432:83-89.

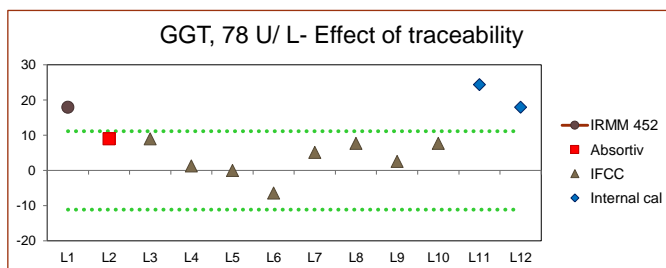
1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

✓ EQA

% deviation to reference-method value (SKML 1st pilot)
10 Spanish participants



Perich C et al. Clin Chim Acta 2014;432:83-89.

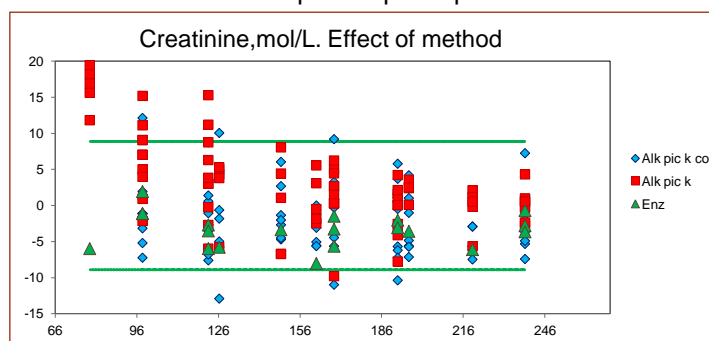
1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

✓ EQA

% deviation to reference-method value (SKML 1st & 2nd pilot)
23 Spanish participants



1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

✓ INDIVIDUALITY INDEX (II)

$$II = CV_I / CV_G$$

- Of the 358 analytes with CV_I and CV_G , 202 (**56%**) have $II \leq 0.6$.



Good for monitoring

Harris EK. Prog Clin Pathol 1971;8:45-66
Fraser CG. Biological Variation: From Principles To Practice. AACC Press 2001

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

✓ REFERENCE CHANGE VALUE (RCV)

$$RCV = 2^{1/2}(CV_A^2 + CV_I^2)^{1/2}$$

Harris EK, Yasaka T. Clin Chem 1983;29:25-30
Fraser CG, Harris EK. Crit Rev Clin Lab Sci 1989;27,5:409-437
Fraser CG. Biological Variation: From Principles To Practice. AACC Press 2001

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation from healthy people Applications and limitations

RCV

Minimum change that should be observed between 2⁽¹⁾ or more⁽²⁾ consecutive results of an analyte to be considered as clinically relevant

⁽¹⁾ Fraser CG. Ann Clin Biochem 2011;49:1-3

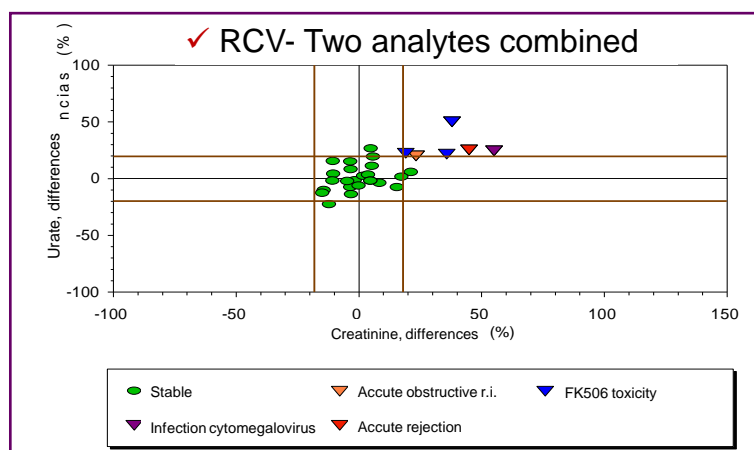
⁽²⁾ Lund F et al. Ann Clin Biochem 2014 DOI: 0004563214534636

⁽²⁾ Lund F et al. Ann Clin Biochem 2014 DOI: 0004563214555163

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



1. Biological variation Applications and limitations



Biosca C et al. Clin Chem 2001;47:2146-48.



1. Biological variation from healthy people Applications and limitations

✓ RCV- Validation of results

Test	Resultat	Marges	I	Anterior	Data	Coment	R	Anak	Flag	Reg
San-Leucòcits	8,8	4,5 - 11,5	7,2	18/05/2009					Penr.	OL
San-Neutòfils	53,5	40,0 - 80,0	53,1	18/05/2009					Penr.	OL
San-Limfòcits	35,8	15,0 - 50,0	36,7	18/05/2009					Penr.	OL
San-Monòcits	7,2	2,0 - 11,0	6,8	18/05/2009					Penr.	OL
San-Eosinòfils	2,9	1,0 - 6,0	2,4	18/05/2009					Penr.	OL
San-Basòfils	0,6	0,0 - 2,0	1	18/05/2009					Penr.	OL
Suma	100,00	100,00 - 100,00	100	18/05/2009					Penr.	CA
Glucose	94	70 - 110							PSM	N OL
Creatinina	1,2	0,65 - 1,25	1,01	18/05/2009					PSM	N OL
MDRD-IDMS	60	> 60	60	18/05/2009						CA
Colesterol	198	142 - 240	183	16/06/2009					PSM	N OL
HDL-Colest	64	> 35	60	16/06/2009					PSM	N OL
LDL	122	< 160	110	16/06/2009					PSM	CA
Triglicèrid	60	44 - 200	65	16/06/2009					PSM	N OL
ALT	14	< 41	14	18/05/2009					PSM	N OL
Hemolitzal Mod	7	0 - 25	8	16/06/2009					PSM	N OL
Ictèric Modular	1	0 - 5	2	16/06/2009					PSM	N OL
Lipèmic Modular	10	0 - 145	4	16/06/2009					PSM	N OL
Est. Basic S. nou	OK	OK	OK	18/05/2009						OL
Dialipm. seguim	OK	OK	OK	16/06/2009						OL

1. Biological variation from healthy people Applications and limitations

✓ RCV- Reporting to clinicians

NINEWELLS HOSPITAL AND MEDICAL SCHOOL				
	Result		Units	Ref. values
Sodium	138	*	mmol/L	135-147
Potassium	5.0		mmol/L	3.5-5.0
Urea	9.5	**	mmol/L	3.3-6.6
Creatinine	137	>	mmol/L	50-100
Bilirubins	100	>>	mmol/L	NAME
Albumin	23	<<	g/L	36-50
Calcium	2.27	**	mmol/L	2.1-2.6

Fraser CG. Biological Variation: From Principles to Practice. Washington, DC, AACC Press, 2001

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014

2. Biological variation from patients What do we know?



✓ Database (DB)

1st DB in disease (2007)

- 66 analytes
- 34 disease status

2nd DB in disease (2014)

- 97 analytes
- 41 disease status

- Ricós et al. Ann Clin Biochem 2007;44:343-352
- Ricós et al. <http://www.westgard.com/biological-variation-in-patients-with-disease.htm>.

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



2. Biological variation from patients What do we know?

Liver

- Cirrhosis
- Chronic pathology
- Hepatocellular carcinoma
- **Hepatitis**
- **Liver post transplantation**
- **Non-alcoholic fatty liver disease**

Bone

- Osteoporosis
- Bone metabolism disorders
- Paget

Neoplasia

- Breast
- Colorectal
- Hepatocellular
- Lung
- **Melanoma**
- Ovarian
- Prostatic
- **Testicular**



Heart

- Coronary disease
- Myocardial infarction

Kidney

- Chronic renal disease
- Renal post-transplantation

Diabetes Mellitus

- Insulin dependent
- Non insulin dependent

Lipid

- Metabolic lipid disorders
- Hypercholesterolemia

Various

- Cystic fibrosis
- Hypertension
- Hypothyroidism
- **Metabolic syndrome**
- **Monoclonal gammopathy**
- Pregnancy
- Porphyria



2. Biological variation from patients. How should they be used?

CV_I pathology > CV_I healthy individuals, only for:

Pathology	Analyte
Breast carcinoma	Alkaline phosphatase, calcium, CA 15.3, CEA, osteocalcin
Cirrhosis, hepato cellular carcinoma	α -fetoprotein
Chronic liver disease	GGT
Chronic renal disease in children	Creatinine
Diabetes Mellitus type I	Glucose, HbA1C, lipoprotein a, microalbumin
Hepatitis B	α_2 Macroglobulin
Lung carcinoma	CA 125, CA 19.9, CEA
Ovarian carcinoma	CA 125, CA 19.9
Paget	Alkaline phosphatase

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Overview - BV application

- Q specifications based on BV are widely used and have been included in various QC programs designed to optimize operative rules.
- They have been incorporated in EQA reports.
- The RCV is not so well implemented because of insufficiently developed LIMS.

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Overview - BV database

PROS

- There is a criterion for accepting data
 - Only specifically designed papers
 - $PI = CV_A / 0.5 CV_I$
 $PI > 2 \rightarrow$ rejected
 - CV_I, CV_G estimated by ANOVA or Fraser & Harris
- Data are systematically updated every two years

Perich C et al. CCLM 2014 aop (DOI 10.1515/cclm-2014-0739)

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Overview – BV database

WEAKNESS

- No data for many analytes paucity of publications available for inclusion in the database
- Few data for some analytes

# Publications	# Analytes
More than 10	27
Between 9 and 2	129
Only 1	202

Perich C et al. CCLM 2014 aop (DOI 10.1515/cclm-2014-0739)

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



Overview - BV database

WEAKNESS

- Derived quality specification too restrictive for some analytes as compared with current technological capability (s-sodium, albumin and chloride and blood HbA_{1c})
- And too permissive for others with high biological variation (s- C-reactive protein, triglycerides and urea)

Perich C et al. CCLM 2014 aop (DOI 10.1515/cclm-2014-0739)

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014



CONCLUSIONS

BV - DATABASE

- Preparing international guidelines on how to estimate BV based on data available on the LIMS.
- Developing an international criteria to select the more reliable publications dealing with estimation of the components of BV.
- We are ready and willing for collaboration with such worthy initiatives.

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014





Thank you so much!

1st EFLM Strategic Conference- Analytical performance goals 15y after Stockholm. Milan 24-25 Nov 2014

