



Les « reference change values », vers une nouvelle expression des résultats de laboratoire? Application aux marqueurs de fibrose hépatique

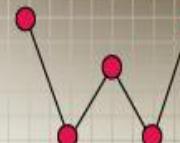
Nicolas Istaces

Laboratoire de Chimie Médicale
Hôpital Erasme

<http://www.westgard.com/biodatabase1.htm>

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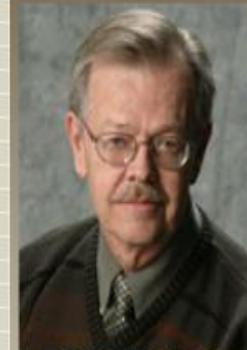
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Blog

HOME > ESSAYS > GUEST ESSAY > BIOLOGIC VARIATION DATABASE, THE 2014 UPDATE

BIOLOGIC VARIATION DATABASE



Celebrate 15 years of evidence-based quality goals! The 8th update of the biologic variation database, with updated specifications and new analytes for 2014.

Biological variation database, and quality specifications for imprecision, bias and total error (desirable and minimum). The 2014 update

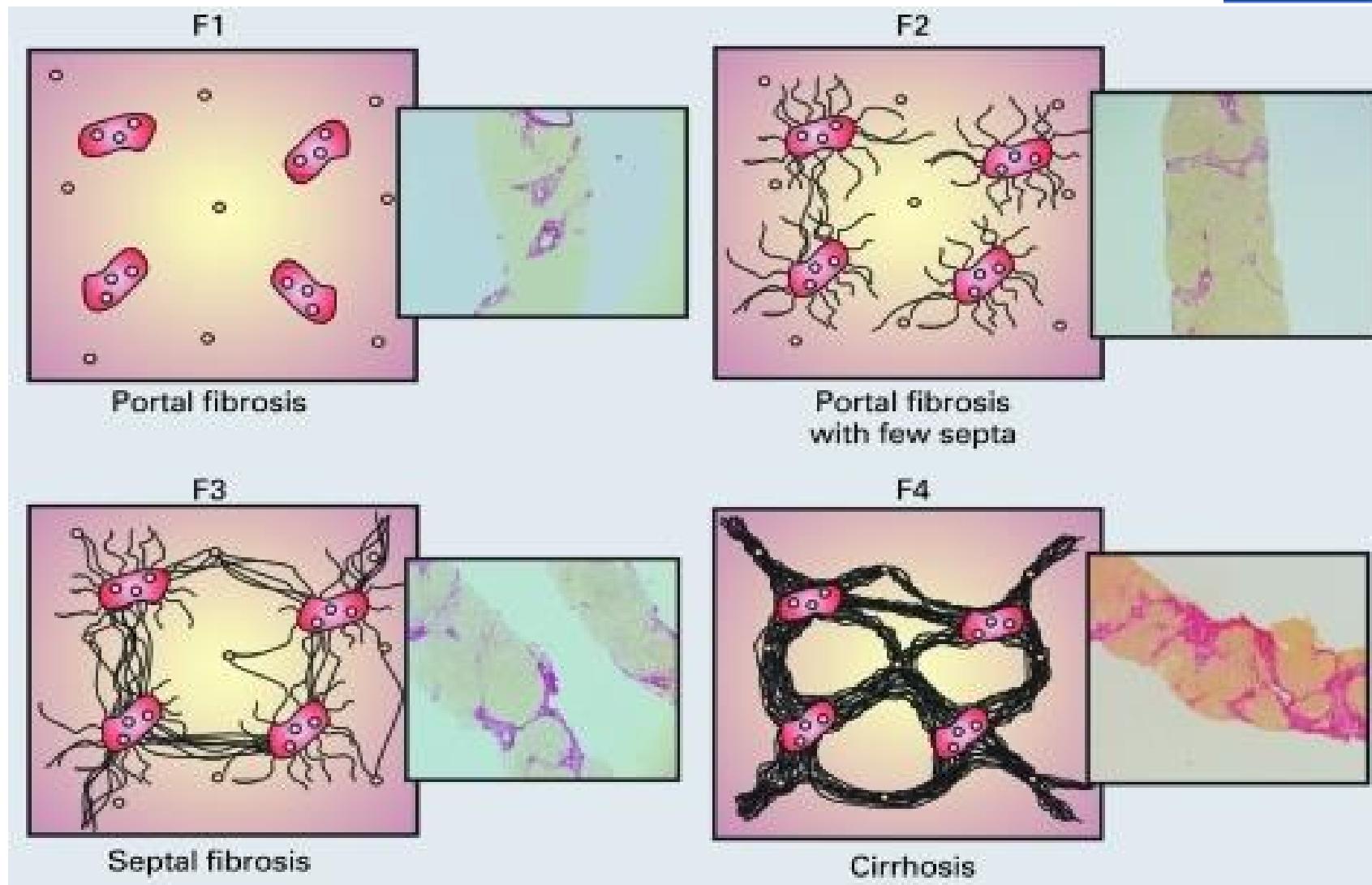
 

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Score METAVIR : système de stadification histo-pathologique de fibrose hépatique

From Asselah et al. Gene expression and hepatitis C virus infection. Gut 2009

Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994

FibroTest (FT)

- “ Index (de 0.00 à 1.00) basé sur :
 - L’âge (années) et le sexe du patient
 - Résultats de dosage : **α2-macroglobuline, haptoglobine, γ-GT, bilirubine totale et apolipoprotéine A1**

$$z = 4.467 \times \log_{10}[\alpha 2\text{macroglobulin}(g/L)] - 1.357 \times \log_{10}[\text{Haptoglobin}(g/L)] + 1.017 \times \log_{10}[\text{GGT}(IU/L)] + 0.0281 \times [\text{Age}(years)] \\ + 1.737 \times \log_{10}[\text{Bilirubin}(\mu\text{mol}/L)] - 1.184 \times [\text{ApoA1}(g/L)] + 0.301 \times \text{Sex}(\text{female} = 0, \text{male} = 1) - 5.54$$

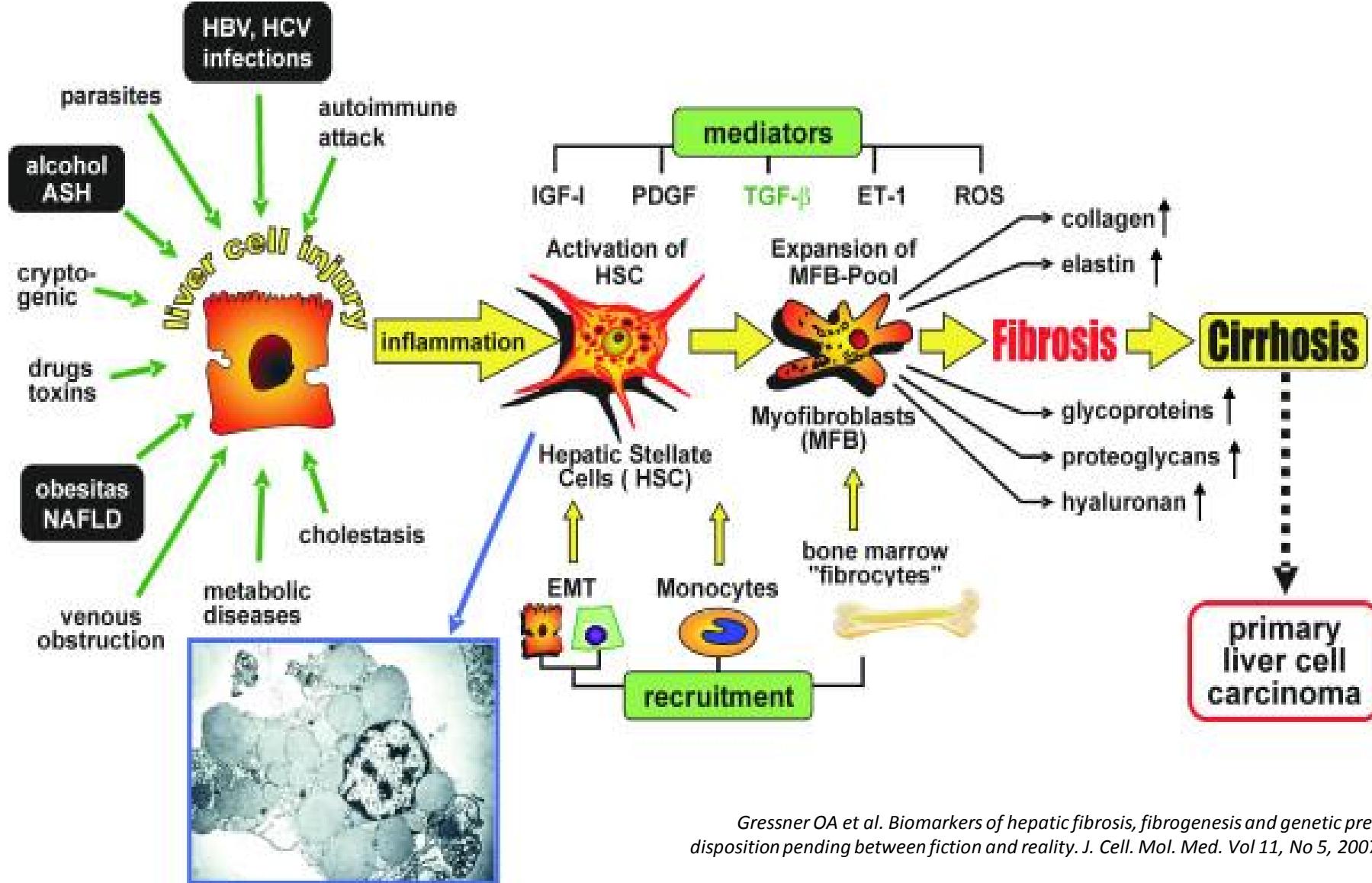
*Imbert-Bismut F et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet. 2001
Pojnard T et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. BMC Gastroenterol. 2007*

Biomarkers of liver cell injury
ALT, AST, GLDH,
 γ GT, LDH5 ...

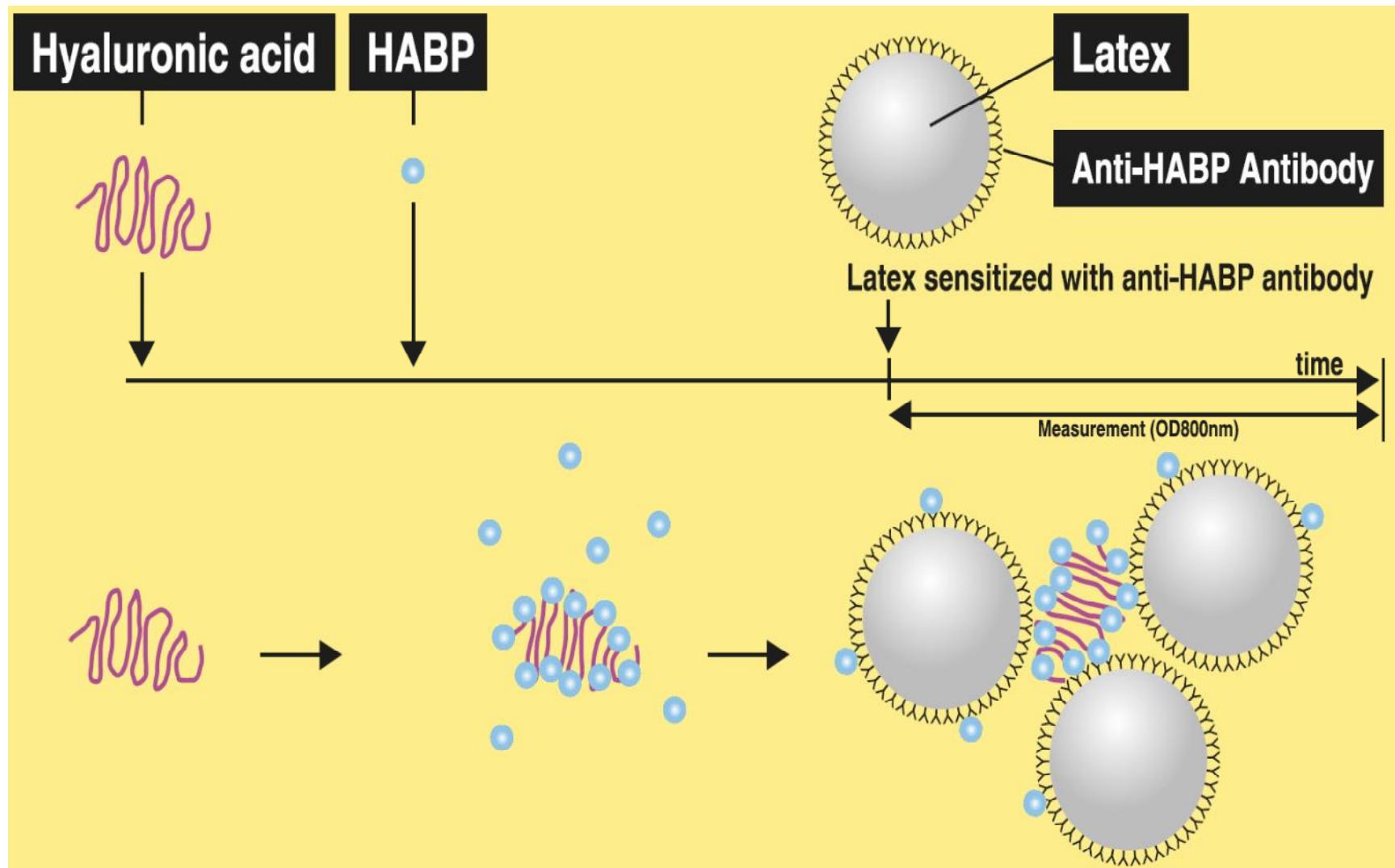
Biomarkers of inflammation
CRP, α -M,
haptoglobin,
chemokines

Biomarkers of fibrogenesis
fibrogenic cytokines, CTGF,
circulating fibrocytes, CSF,
chemokines

**Biomarkers of fibrosis
and ECM-turnover**
hyaluronan, PIIINP,
MMPs, TIMPs, laminin



Gressner OA et al. Biomarkers of hepatic fibrosis, fibrogenesis and genetic predisposition pending between fiction and reality. J. Cell. Mol. Med. Vol 11, No 5, 2007

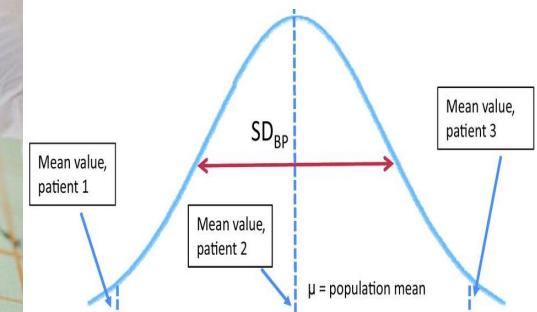
Méthode immunoturbidimétrique par agglutination au latex (AH)

2. Variation biologique et reference change values

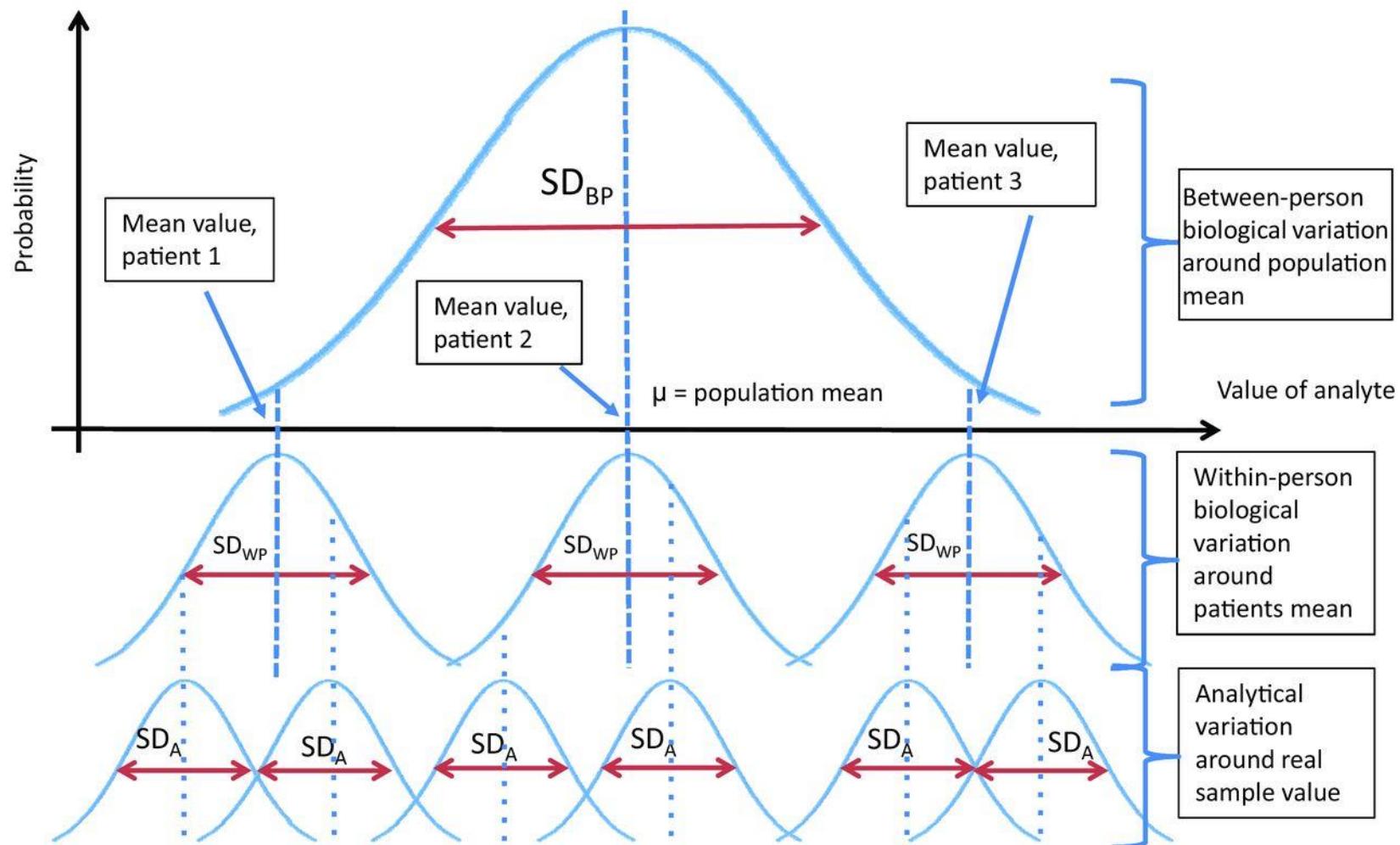
Généralités

- “ Sources de variation d'un résultat d'une méthode d'analyse de laboratoire :
- Variabilité **pré-analytique** : prélèvement, transport et conservation
- Variabilité **analytique** : imprécisions intra-run et inter-run ($CV_{A\ W-R}$ et $CV_{A\ B-R}$)
- Variabilité **biologique** : intra- et interindividuelles (CV_W et CV_B)

Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci. 1989



Nested ANOVA à deux niveaux



2. Variation biologique et reference change values

Généralités

“ Reference change value (RCV) :



$$RCV = 2^{1/2} \times Z \times (CV_A^2 + CV_W^2)^{1/2}$$

But du travail



Etude la variation biologique :

- De l'acide hyaluronique chez des individus atteints de **maladie hépatique chronique (MHC)**, stratifiés selon :
 - ❑ L'étiologie (CHC, CHB, NAFLD)
 - ❑ Le stade de fibrose (F0-F1, F2, F3)
- Du FibroTest, de ses 5 analytes, et de l'acide hyaluronique chez des **volontaires sains**

Méthodes statistiques

Stabilité de l'AH :

- Test t pairé (10 échantillons)

Lazarova E et al. Automated quantification of serum hyaluronic acid for non-invasive assessment of liver fibrosis in chronic hepatic diseases. Immuno-analyse & Biologie Spécialisée 2011

- Non-significatif ($p=0.2751$) ➔ stabilité à -80°C (38 mois)

Identification des outliers :

- Test de Grubbs ($\alpha=0.05$)
- Remplacement par la moyenne des résultats restants

$$Z = \frac{|\text{mean} - \text{value}|}{\text{SD}}$$

Nested ANOVA :

- Isolation des $\text{CV}_{A\text{W-R}}$, CV_w et CV_B
- Index d'individualité ($\text{CV}_{W+A} / \text{CV}_B$) et index de performance ($\text{CV}_{A\text{W-R}} / \text{CV}_w$)
- Nombre d'échantillons pour évaluer le setpoint homéostatique

RCV :

- $\text{CV}_{A\text{B-R}}$: AH (duplicates échantillons QC : 5 runs), analytes FT (QC Erasme), FT

Imbert-Bismut F et al. Intra-laboratory analytical variability of biochemical markers of fibrosis (Fibrotest) and activity (Actitest) and reference ranges in healthy blood donors. Clin. Chem. Lab. Med. 2004

- Approches normale et lognormale ($\alpha=0.05$, bilatéral)

Fraser CG, Harris EK. Generation and application of data on biological variation in clinical chemistry. Crit Rev Clin Lab Sci. 1989

Fokkema MR et al. Reference change values for brain natriuretic peptides revisited. Clin. Chem. 2006

$$\text{mean} = \exp\{\mu + \frac{1}{2}\sigma^2\}$$

$$SD = \exp\{\mu + \frac{1}{2}\sigma^2\}\sqrt{\exp(\sigma^2) - 1}$$

$$CV = \sqrt{\exp(\sigma^2) - 1}$$

Biological Variation and Reference Change Value of High-Sensitivity Troponin T in Healthy Individuals during Short and Intermediate Follow-up Periods

Lutz Frankenstein,^{1,*} Alan H.B. Wu,² Klaus Hallermayer,³ Frank H. Wians, Jr.,⁴ Evangelos Giannitsis,¹ and Hugo A. Katus¹

$$CV_i = (CV_i^2 - CV_a^2)^{1/2}.$$

Clinical Chemistry 57:7
1068–1071 (2011)

$$\sigma = [\ln(CV_t^2 + 1)]^{1/2}.$$

$$RCV_{\text{pos}} = [\exp(1.96 \times 2^{1/2} \times \sigma) - 1] \times 100$$

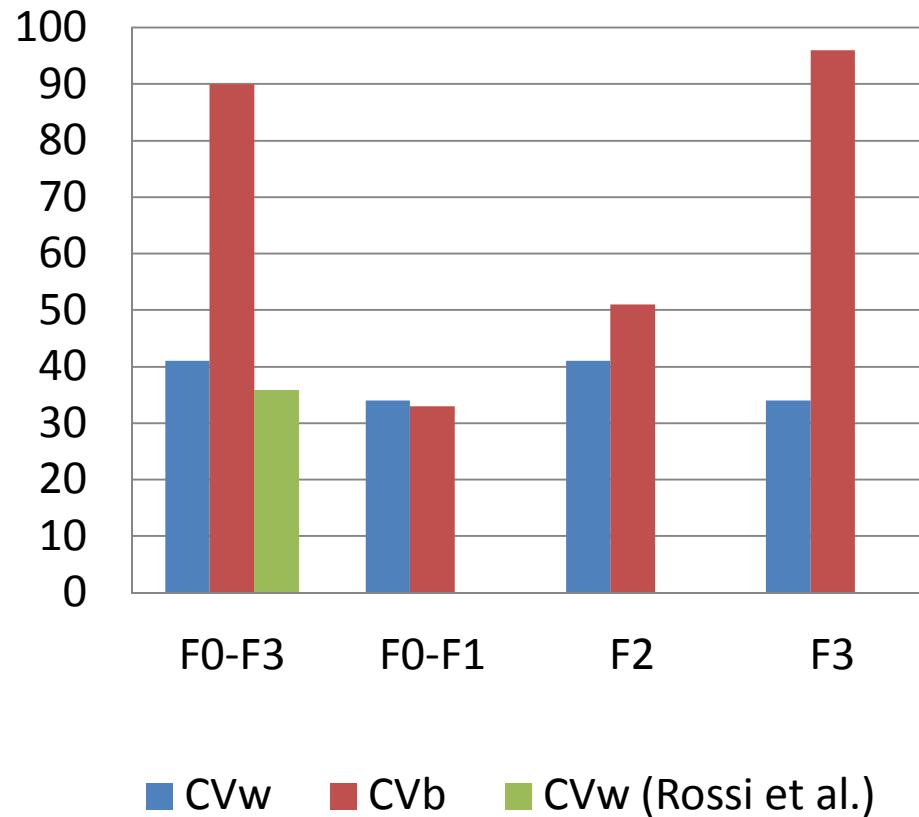
$$RCV_{\text{neg}} = [\exp(-1.96 \times 2^{1/2} \times \sigma) - 1] \times 100$$

Résultats

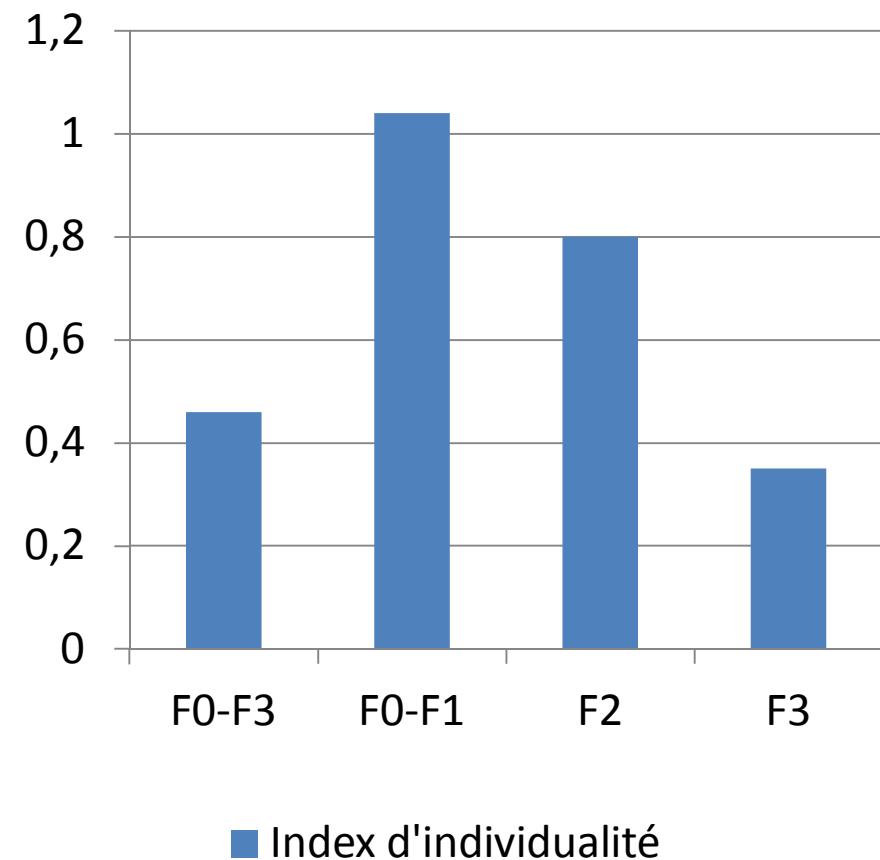
NAFLD : CV_w , CV_b et index d'individualité (AH)



NAFLD : CV_w , CV_b (%)



Index d'individualité

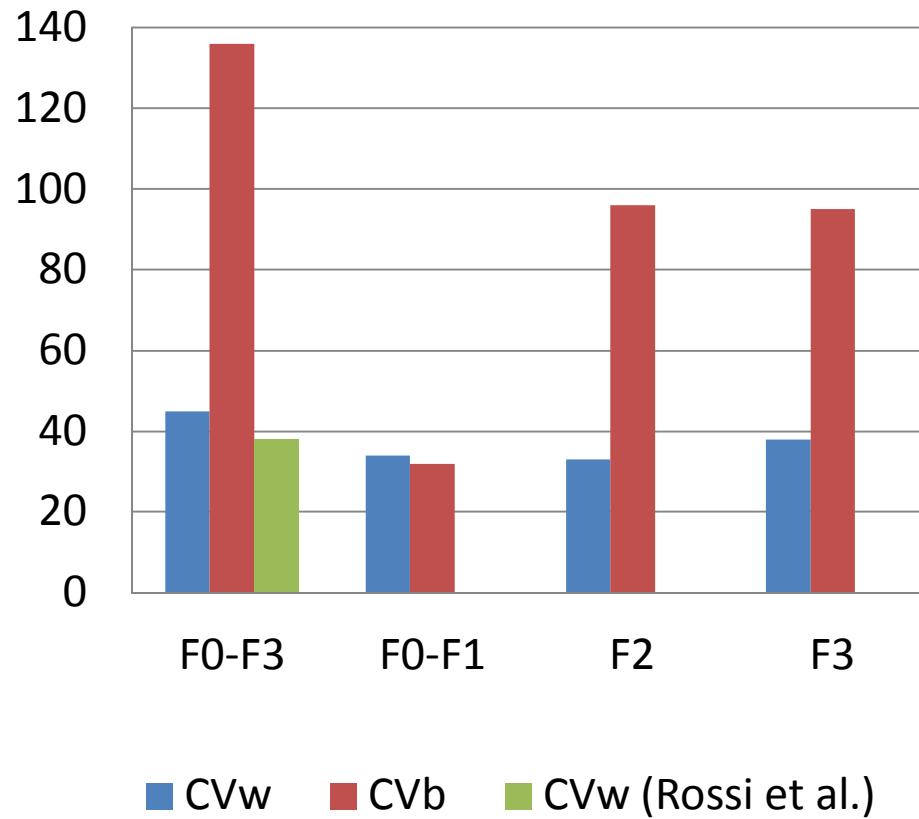


Résultats

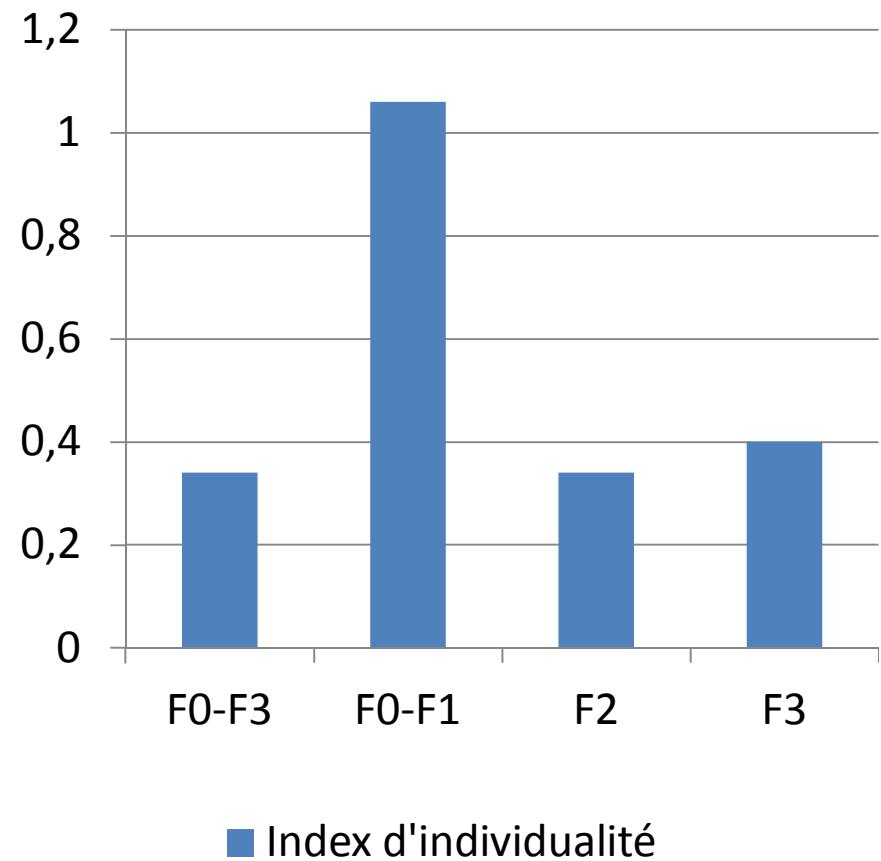
CHC : CV_w , CV_b et index d'individualité (AH)



CHC : CV_w , CV_b (%)



Index d'individualité



Fibrosis Progression in Chronic Hepatitis C: Morphometric Image Analysis in the HALT-C Trial



NIH Public Access
Author Manuscript

Hepatology. Author manuscript; available in PMC 2013 July 10.

Zachary D. Goodman¹, Anne M. Stoddard², Herbert L. Bonkovsky³, Robert J. Fontana⁴,

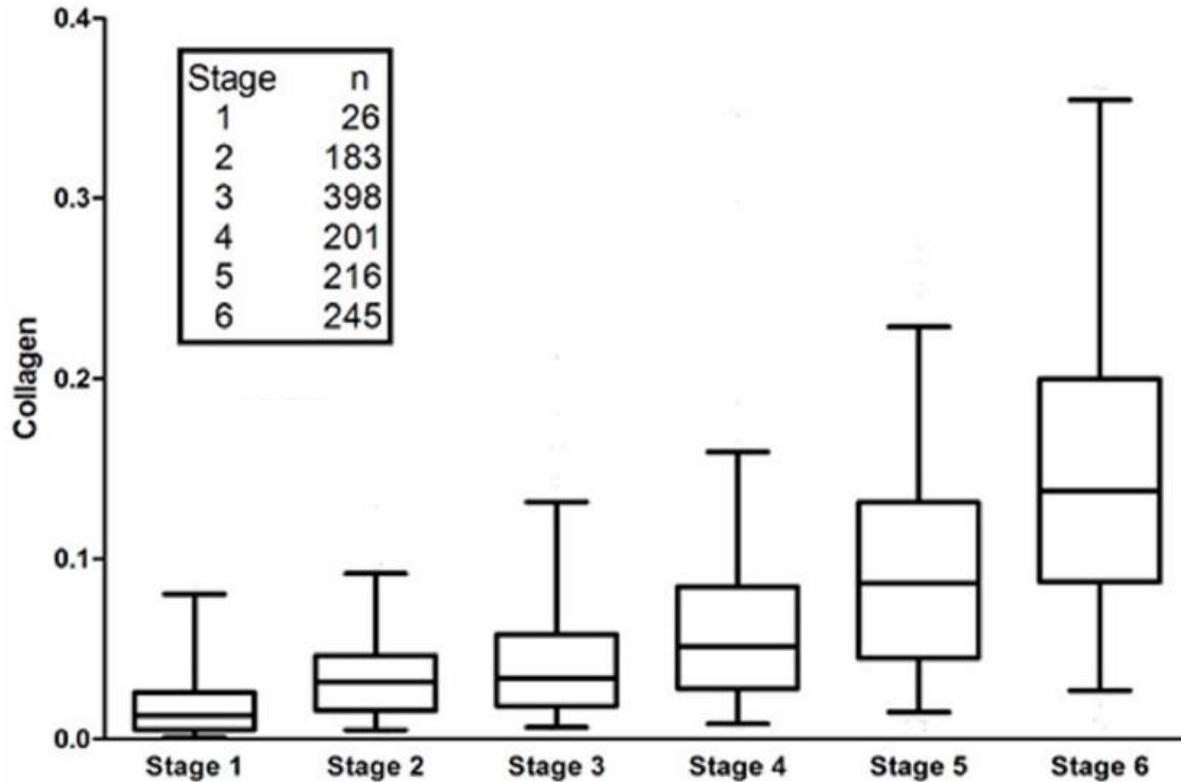


Figure 3.

Distribution of measurements of collagen content at each Ishak fibrosis stage for the 1269 liver biopsies in the study. The boxes show the median, 25th and 75th percentiles, whereas the lines 2.5 and 97.5 percentiles (outliers not shown).

Conclusion :

"Morphometry demonstrated complex, nonlinear changes in fibrosis over time" (baseline, 18 months and another 24 months)

"Because chronic hepatitis C takes decades to evolve into cirrhosis, and even longer to progress towards decompensation, demonstration of survival benefit resulting from antiviral therapy would require large treatment trials of very long duration"

Variation biologique et RCVs : autres analytes, autres situations cliniques...



- „ MGUS
- „ HbA1c
- „ BNP
- „ hS Troponin
- „ Paramètres hématologiques : cas particulier
- „ ...

Long-Term Biological Variation of Serum Protein Electrophoresis M-Spike, Urine M-Spike, and Monoclonal Serum Free Light Chain Quantification: Implications for Monitoring Monoclonal Gammopathies



Jerry A. Katzmann,^{1,2*} Melissa R. Snyder,¹ S. Vincent Rajkumar,^{1,2} Robert A. Kyle,^{1,2} Terry M. Therneau,
Joanne T. Benson,³ and Angela Dispenzieri^{1,2}

Clinical Chemistry 57:12 (2011)

Table 4. Total, analytical, and biological CVs.^a

	Measurable serum M-spike ^b	Urine M-spike (≥ 200 mg/24 h)	Measurable serum iFLC ^c	Serum IgG
Total CV	8.1	35.8	28.4	13
Analytical CV	2.1	4.5	5.8	4.2
Biological CV	7.8	35.5	27.8	12.3

^a Total CVs are from Table 2, analytical CVs are from laboratory validation studies, and biological CVs are derived from the relationship of the biological CV being equal to the square root of the difference of the square of the total CV minus the square of the analytical CV.

^b Values >10 g/L.

^c Values >100 mg/L.

Variation biologique et RCVs : autres analytes, autres situations cliniques...

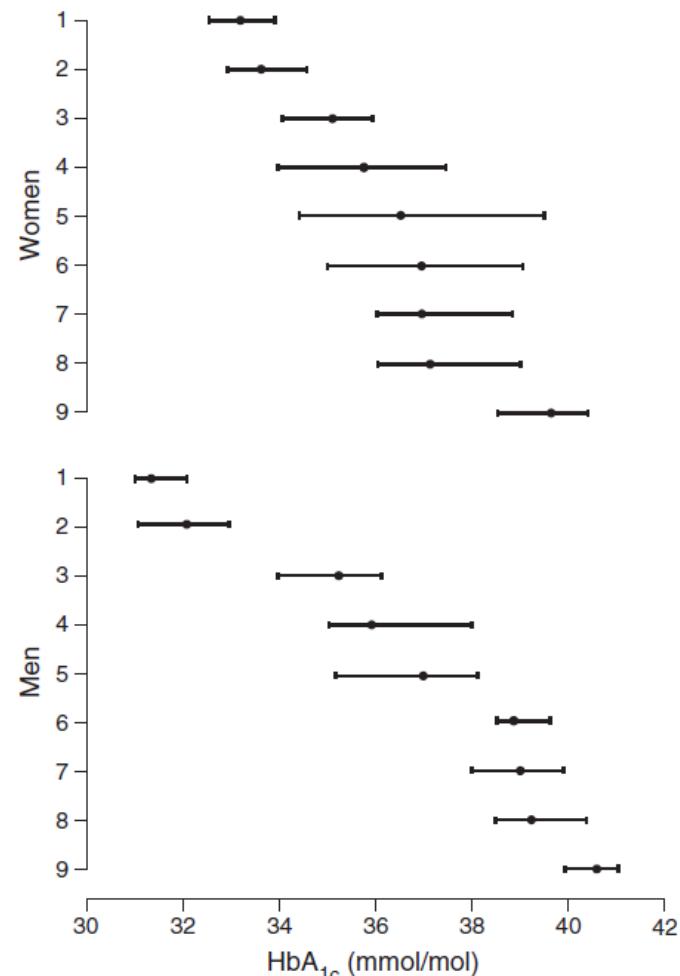


Fig. 1. Individual parametric mean and absolute range of HbA_{1c} values in studied subjects.

Table 2

Mean values, estimated average variance components and indices derived from data on biological variation of HbA_{1c}.

Group	HbA _{1c} , mmol/mol	CV _A , %	CV _I , %	CV _G , %	II	CD, %	n
All	36.3	2.4	2.5	7.1	0.35	9.5	2
Men	36.5		1.9	8.9	0.21		
Women	36.1		3.2	5.1	0.62		

CV_A, CV_I, CV_G, II, CD and n as explained in Table 1.

Revaluation of biological variation of glycated hemoglobin (HbA_{1c}) using an accurately designed protocol and an assay traceable to the IFCC reference system

Clinica Chimica Acta 412 (2011) 1412–1416

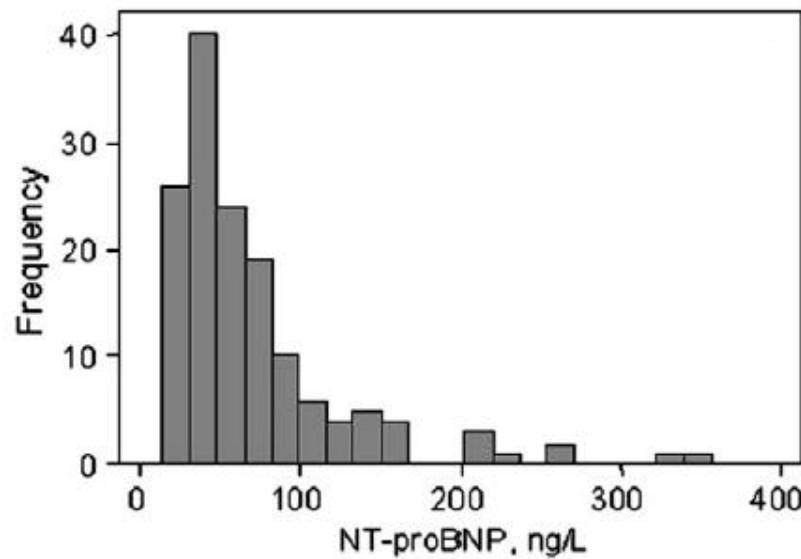
“One of the major limitations most frequently found in previous studies on HbA1c biological variation was the recruitment of diabetic patients. The presence of disease, mainly if unstable and not well controlled, may significantly amplify the fluctuation of HbA1c concentrations in blood around the set point, markedly modifying both components (intra- and inter-individual) of biological variation”

Variation biologique et RCVs : autres analytes, autres situations cliniques...

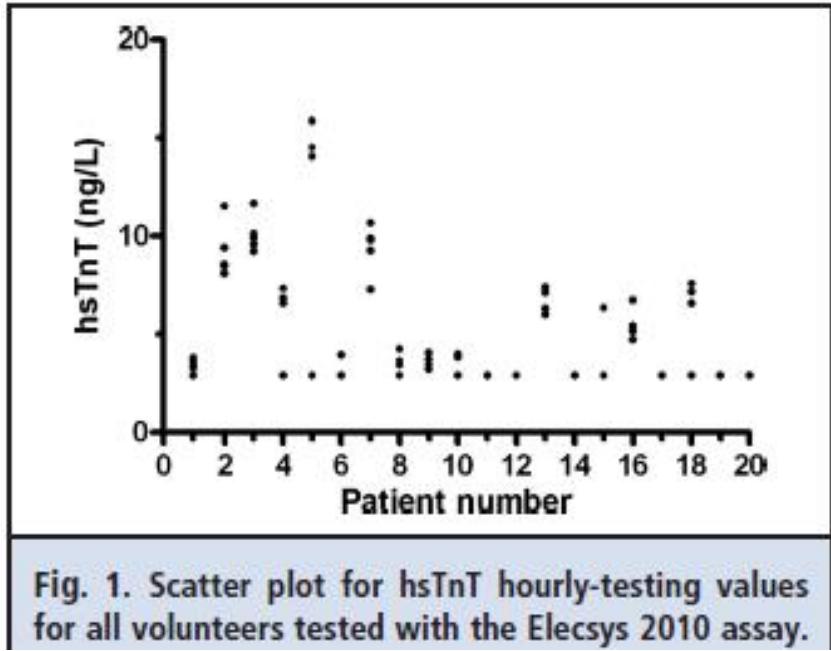


Advantages of the lognormal approach to determining reference change values for N-terminal propeptide B-type natriuretic peptide

C. Klersy et al. / Clinica Chimica Acta 413 (2012) 544–547



Variation biologique et RCVs : autres analytes, autres situations cliniques...



"Acute myocardial infarction is defined by a troponin concentration 99th percentile with an acute increase and/or decrease"

"A change $\geq 20\%$ has been suggested for patients with cardiac troponin already elevated at baseline"

Biological Variation and Reference
Change Value of High-Sensitivity
Troponin T in Healthy Individuals
during Short and Intermediate Follow-up
Periods

Clinical Chemistry 57:7 (2011)

Table 1. Analytical and biological variation of hsTnT.^a

Variable	E 170 assay		Elecsys 2010 assay	
	Hourly	Weekly	Hourly	Weekly
No. of values ^b	98	100	62	56
CV _a , %	7.8	7.8	9.7	9.7
CV _i , %	15 (0.0–66)	31 (6.0–127)	21 (7.4–47)	30 (0.0–97)
CV _b , %	18 (7.1–66)	32 (11–128)	24 (12–48)	32 (8.9–97)
RCV, %				
Normal	± 47	± 87	± 62	± 86
Lognormal	64, -39 (51)	138, -58 (98)	90, -47 (68)	135, -58 (96)

Biological Variations of Hematologic Parameters Determined by UniCel DxH 800 Hematology Analyzer



Arch Pathol Lab Med—Vol 137, August 2013

Table 1. Biological Coefficients of Variation of Hematologic Parameters

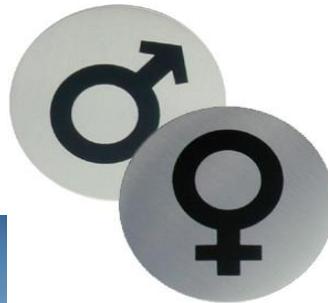
Analytes	CV _A , %		CV _I , %		CV _{Gr} , %		II	
	This Study	Ricos et al, ² 1999	This Study	Ricos et al, ² 1999	This Study	Ricos et al, ² 1999	This Study	Ricos et al, ² 1999
Erythrocytes								
RBC	0.10	1.60	3.04	3.20	10.94	6.10	0.0750	0.5246
Hemoglobin	0.32	1.40	2.44	2.80	11.25	6.60	0.2000	0.4242
Hematocrit	0.24	1.40	2.44	2.80	10.34	6.40	0.2000	0.4375
MCV	0.10	0.70	1.12	1.30	7.10	4.80	0.1577	0.2708
MCH	0.17	0.80	1.31	1.60	8.26	5.20	0.1574	0.3077
MCHC	0.15	0.90	0.82	1.70	2.05	2.80	0.3902	0.6071
RDW CV	1.10	1.80	1.49	3.50	8.79	5.70	0.1695	0.6140
RDW SD	0.87	NA	1.27	NA	4.45	NA	0.2854	NA
LHD	4.54	NA	14.62	NA	19.64	NA	0.7444	NA
MAF	0.35	NA	3.72	NA	14.92	NA	0.2493	NA
MSCV	0.86	NA	1.75	NA	7.45	NA	0.2349	NA
RSF	0.45	NA	0.74	NA	6.31	NA	0.1173	NA
Reticulocytes								
Reticulocyte No.	9.13	NA	9.60	NA	33.71	NA	0.2848	NA
Reticulocyte %	9.02	NA	9.47	NA	30.63	NA	0.2800	NA
IRF	6.79	NA	8.45	NA	16.77	NA	0.2000	NA
MRV	0.87	NA	1.64	NA	5.80	NA	0.1500	NA
HLR No.	3.64	NA	11.49	NA	44.55	NA	0.2579	NA
HLR %	9.52	NA	11.68	NA	42.07	NA	0.2776	NA
RDWR CV	1.61	NA	5.72	NA	8.08	NA	0.7079	NA
RDWR SD	1.47	NA	6.07	NA	6.96	NA	0.8721	NA
Platelets								
Count	1.37	4.60	5.27	9.10	26.57	21.90	0.1983	0.4155
MPV	0.47	2.20	2.12	4.30	11.26	8.10	0.1883	0.5309
PDW	0.35	1.40	0.75	2.8	3.25	NA	0.2308	NA

Abbreviations: CV, coefficient of variation; CV_A, analytical coefficient of variation; CV_{Gr}, between-subject biological coefficient of variation; CV_I, within-subject biological coefficient of variation; HLR, high-light-scatter reticulocytes; II, index of individuality (ratio of CV_I;CV_{Gr}); IRF, immature reticulocyte fraction; LHD, low hemoglobin density; MAF, microcytic anemia factor; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; MRV, mean reticulocyte volume; MSCV, mean spheroid cell volume; NA, not available; PDW, platelet distribution width; RBC, red blood cell; RDW, red cell distribution width; RDWR, reticulocyte distribution width; RSF, red cell size factor.

Variation biologique et RCVs : les pièges à éviter...



“ Choix des sujets



Variation biologique et RCVs : les pièges à éviter...

ULB

Choix du nombre d'individus, d'échantillons par individus

Table 3. Power for detection of the SD_{WP} for different experimental designs with varying numbers of individuals, samples, and replicates for different ratios between SD_A and SD_{WP} .

		Ratio between analytical and within-person biological variation											
Individuals	Samples	1			1.5			2			3		
		Replicates			Replicates			Replicates			Replicates		
Individuals	Samples	2	3	4	2	3	4	2	3	4	2	3	4
10	2	0.65	0.87	0.95	0.32	0.55	0.70	0.19	0.33	0.46	0.11	0.15	0.20
	4	0.94	1.00	1.00	0.59	0.87	0.97	0.33	0.60	0.79	0.15	0.26	0.38
	6	0.99	1.00	1.00	0.76	0.97	1.00	0.44	0.76	0.92	0.18	0.34	0.51
	8	1.00	1.00	1.00	0.86	0.99	1.00	0.54	0.87	0.97	0.22	0.41	0.62
	10	1.00	1.00	1.00	0.92	1.00	1.00	0.63	0.93	0.99	0.25	0.49	0.71
15	2	0.80	0.96	0.99	0.43	0.69	0.84	0.24	0.41	0.58	0.12	0.19	0.26
	4	0.99	1.00	1.00	0.74	0.96	0.99	0.42	0.74	0.90	0.18	0.32	0.49
	6	1.00	1.00	1.00	0.89	1.00	1.00	0.57	0.89	0.98	0.23	0.45	0.65
	8	1.00	1.00	1.00	0.96	1.00	1.00	0.69	0.96	1.00	0.29	0.55	0.76
	10	1.00	1.00	1.00	0.99	1.00	1.00	0.78	0.98	1.00	0.32	0.63	0.84

Røraas T et al. 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

Variation biologique et RCVs : les pièges à éviter...



- ” Nécessité de standardisation des méthodes expérimentales et statistiques :
- IC95%
- Comparer RCV entre études seulement si même méthode de dosage, sinon se limiter à comparer CV_w et index d'individualité

Table 1. Expected width of CI_{95} for the SD_{WP} (in % of the SD_{WP}) with varying numbers of individuals, samples, and replicates for different ratios between the SD_A and SD_{WP} .

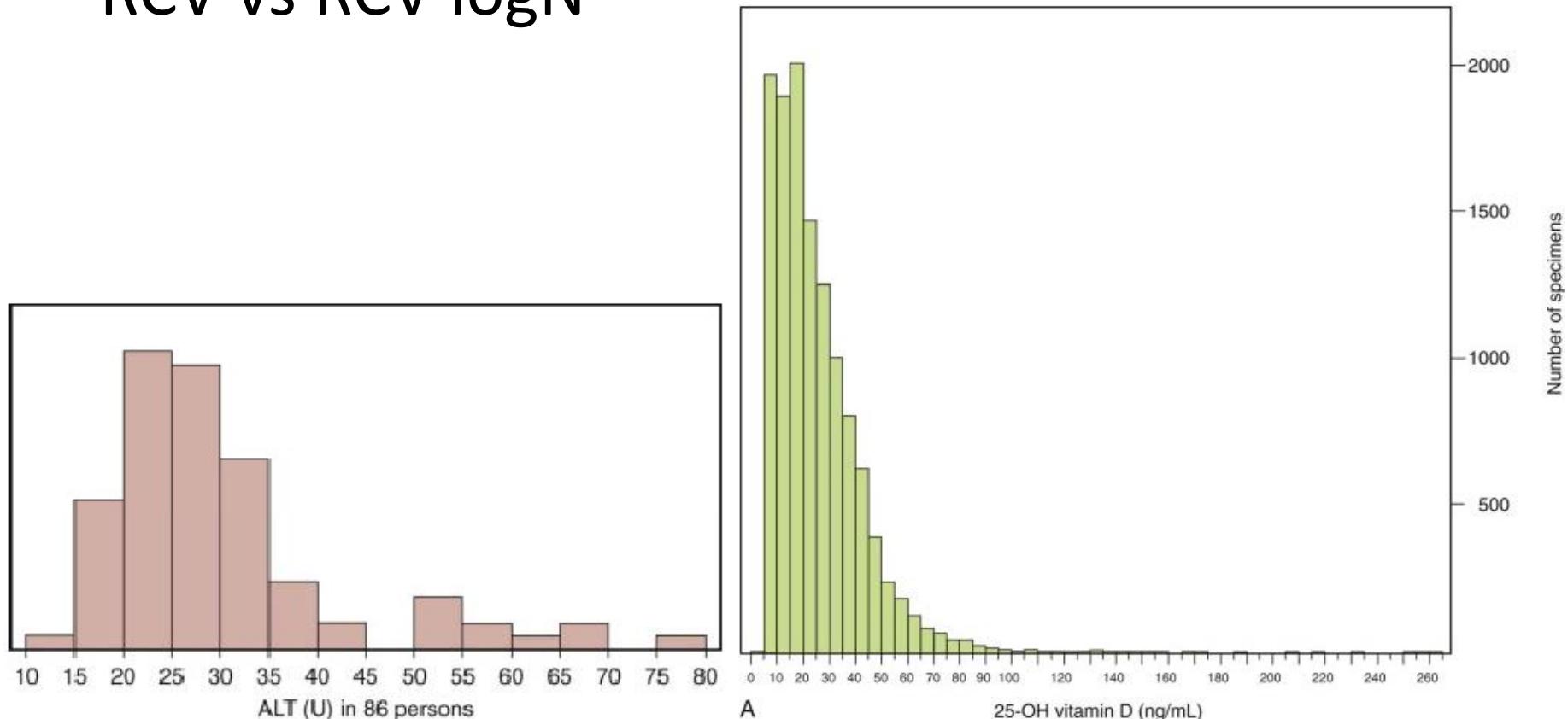
Individuals	Samples	Ratio between analytical and within biological variation																				
		0.25			0.5			0.75			1			1.5			2			3		
		Replicates			Replicates			Replicates			Replicates			Replicates			Replicates			Replicates		
Individuals	Samples	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4	2	3	4
10	2	109	108	107	119	114	112	138	125	119	177	141	131	233	215	167	269	242	227	353	305	278
	4	55	55	55	61	58	57	71	64	61	87	73	67	164	100	86	185	169	115	235	205	189
	6	42	41	41	46	44	43	53	48	46	65	55	51	107	75	65	165	109	86	206	180	168
	8	35	35	35	38	37	36	45	41	39	54	46	43	87	63	54	155	89	71	191	168	142
	10	31	30	30	34	32	32	39	36	34	47	40	37	75	55	48	140	77	63	181	160	115
15	2	83	82	82	91	87	86	105	96	92	129	108	101	199	151	128	228	206	185	296	257	235
	4	44	44	44	49	47	46	56	51	49	68	58	54	113	79	68	168	115	91	211	185	171
	6	34	33	33	37	36	35	43	39	37	52	44	41	82	60	52	153	85	69	188	166	131
	8	28	28	28	31	30	29	36	33	31	44	37	35	68	50	44	115	71	58	175	156	103
	10	25	25	25	27	26	26	32	29	28	38	33	30	60	44	39	96	62	51	168	134	89

Røraas T et al. 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

Variation biologique et RCVs : les pièges à éviter...



” RCV vs RCV logN



From Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd Edition

Variation biologique et RCVs : les pièges à éviter...



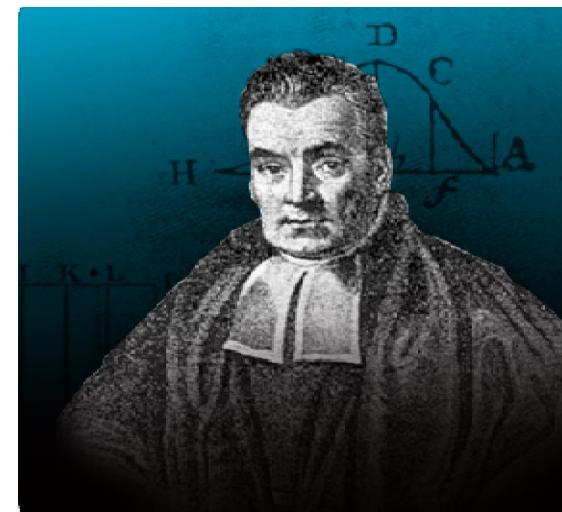
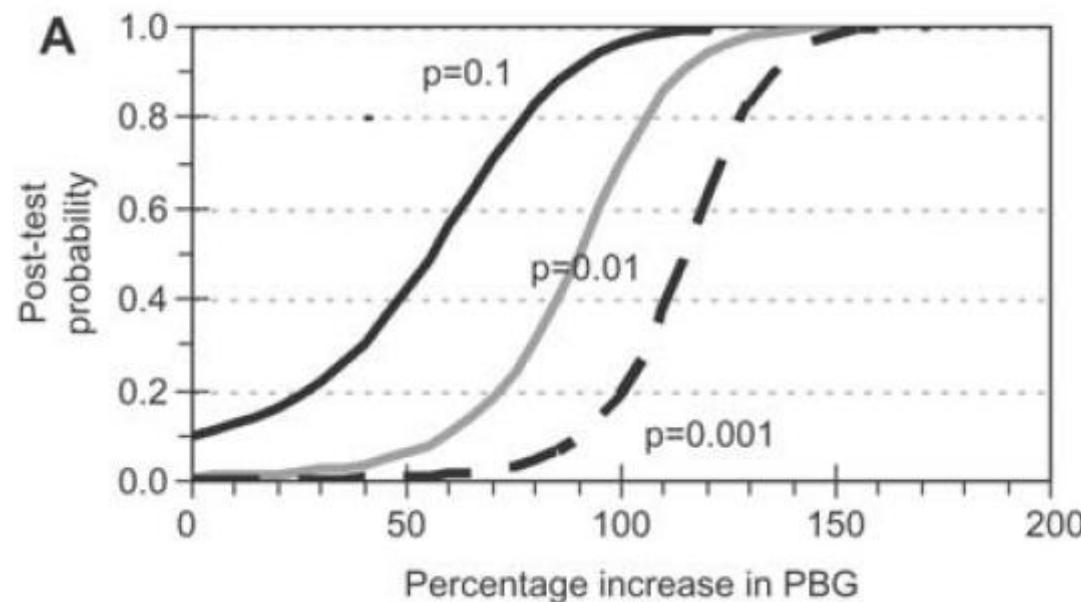
” Les conclusions hâtives...



Variation biologique et RCVs : les pièges à éviter...



“ RCV et approche bayésienne



‘Likelihood-ratio’ and ‘odds’ applied to monitoring of patients as a supplement to ‘reference change value’ (RCV)

Hyltoft Petersen et al. Clin Chem Lab Med 2008;46(2):157–164

Merci pour votre attention

