

International Conference Lab Quality c/o EUROCHEM 2010

Hotel Niels Juel, 25-26 May in Copenhagen, Denmark



- Introduction
- Brain-to-brain info loop
- Medical concepts
- Error management NEXUS
- (Analytical) goals
- Conclusions

Where breaking the limits really matters. Specifications in Clinical Chemistry!

Henk MJ Goldschmidt
Wednesday May 26th 2010



Innovation waves

2010 → time

- Introduction
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- Conclusions



Evaluation protocols

Technicon Immuno F: Evaluation Including Multifactor Design Protocols
 Henk M.J. Goldschmidt, PhD
 Henk A. van Baren, MSc
 Suzanne M.E. Doris, DSc, DTM, MSc, Medical Technologist
 Hans J.P. van Dijkshoorn, PhD, Senior Clinical Chemist
 Hans J.J. van Laarhoven, PhD, Senior Clinical Chemist
 St Elisabeth Hospital, Tilburg, the Netherlands.

A part of an extensive multifactorial design study was conducted to evaluate the performance of using immunochemical methods for the detection of antibodies, including such as enzyme immunoassay (EIA) and radioimmunoassay (RIA). Additionally, the 27 (MFD) protocol was evaluated. The study was designed to assess the quality of the immunochemical methods used in the laboratory. The results of the study are presented in this paper.

The analytical characteristics of the immunochemical methods were evaluated in terms of accuracy, precision, and stability. The results of the study are presented in this paper.

Fig. 1 shows the correlation with the reference method (y-axis) and the actual method (x-axis). The regression equation is $y = 0.95x + 0.05$ and the correlation coefficient is $r = 0.99$.

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
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- ↳ Conclusions



Error frequencies, redefining loop

Klin. Biochem. Metab., 3 (24), 1995, No. 3, p. 131-140

Gross Errors and Work Flow Analysis in the Clinical Laboratory

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Summary

The level of laboratory services with regard to precision, accuracy as well as costs is broadly recognized. Although the presence of gross errors is undeniable, we believe that a proper quantification is needed as well as a protocol to diminish these in a systematic way. A similar reasoning is applicable to turn around times within the clinical laboratory as well as the time elapsing between the thought of requesting a test and receiving the actual test result.

FONA (faults or near accidents) complaints concerning the laboratory (31 external and 102 internal) were investigated in great detail with regard to cause, location and patient effect. Pareto diagrams were used to investigate the relative importance of the various causes resulting in FONA complaints. To quantify the gross error rate of the laboratory, 1272 tests were executed as patient samples by the laboratory without knowing that the analysis had already been performed and an error rate of 2.5% was determined. A classification scheme of gross errors was postulated. To study the compliance level of the laboratory, we did a workflow analysis of several workstations such as haematology routine testing and all STAT requests. Turn-around times were measured, claims defined and delays investigated. Special attention was paid to the effect of human involvement on the error and delay rate. A workflow analysis simulation software programme was applied in an attempt to predict possible laboratory problem areas. It proved to be a valuable tool in quality management. Finally a set of recommendations was proposed to smooth the workflow and decrease the error and delay rates.

Key words: customer satisfaction, information loop, quality control, quality management.

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Error types



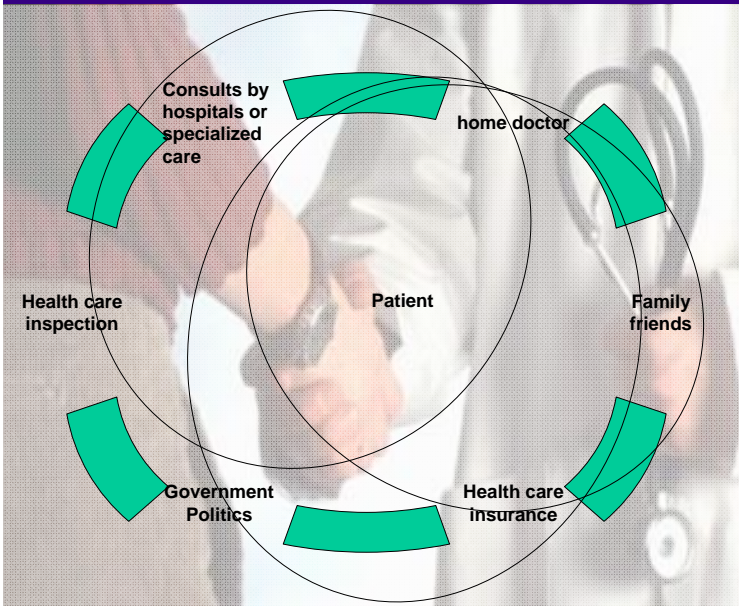
- Random error
- Systematic error
- Sporadic error

- Blunder rate: bandolier

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions

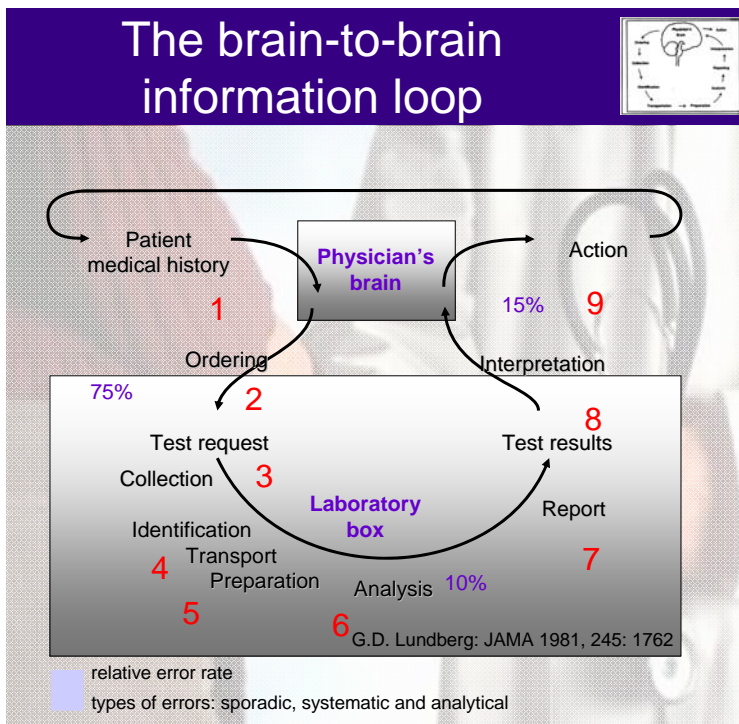


The patient in the lead: all involved

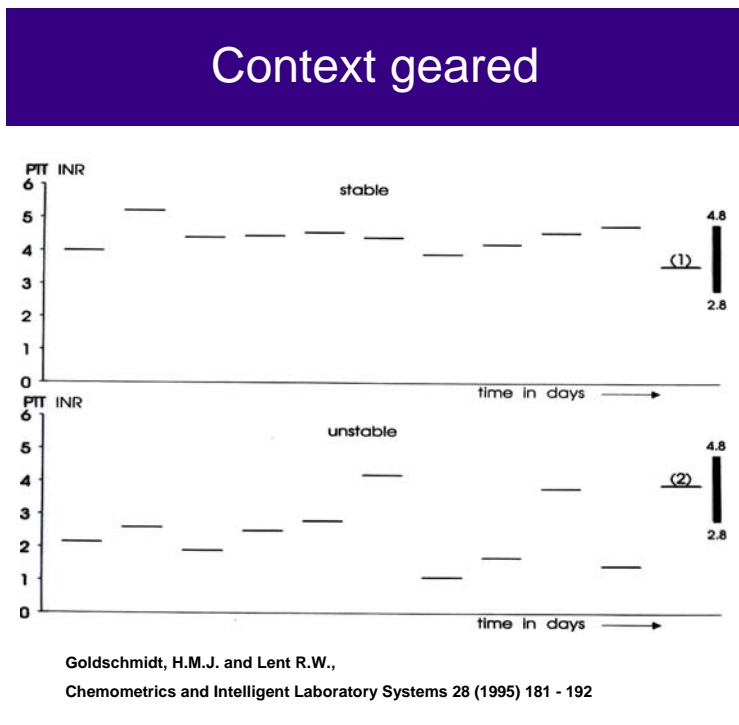


- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions





- ↳ Introduction
- ↳ **Brain-to-brain info loop**
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions

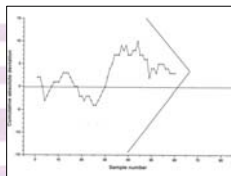
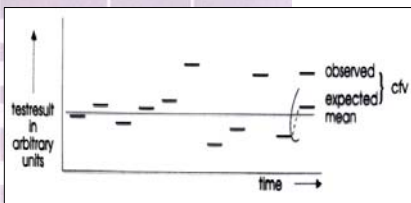


- ↳ Introduction
- ↳ **Brain-to-brain info loop**
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Coagulation

Coagulation	Site:	Method:			
Date Accn#	Analyte/Flag being tested	Results	Problems identified	Changes made	Test performed by
	Normal patient should autoverify				
	PT < 9.2				
	PT > 43.1				
	INR < 0.9				
	INR > 4.4				
	# Delta check PT				
	> 24 hours from collection				
	PTT < 22.3				
	PTT > 37.0				
	# Delta check PTT				
	> 4 hours from collection				
	HPTT < 22.3				
	HPTT > 100.0				
	> 4 hours from collection				
	# Delta check HPPT				
	FGN < 100				
	FGN > 500				
	# Delta check FGN				
	> 8 hours from collection				
	NCD				
	LNCD				
	Difference check				



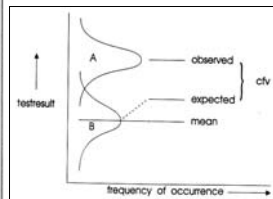
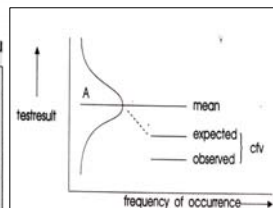
- ↳ Introduction
- ↳ **Brain-to-brain info loop**
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Chemistry / Hematology

Exemple 1 (Biochimie)

Paramètre	Unité	Résultat	Limite inférieure	Limite supérieure
Sodium	mmol/l	139	137	141
Chlorures	mmol/l	113	99	127
Bicarbonates	mmol/l	23	25	29
Protéines	g/l	62	70	78
Balance ion.	mmol/l	97.38	100.7	103.7
Ure	mmol/l	4.35	2.9	6.7
Créatinine	µmol/l	66.3	42.3	108.3
Glucose	mmol/l	4.78	5.56	6.36
Acide urique	µmol/l	460	360	460
Cholestérol	mmol/l	5	5.2	5.4
Triglycérides	mmol/l	1.5	1.33	1.5
Calcium	mmol/l	1.75	1.75	1.75
Phosphore	mmol/l	1.45	1.37	1.45
Fer	µmol/l	15	10	10
Phosphatas. alc.	UI 37°	97	88	88
AST	UI 37°	55	45	45
Bilirubine tot.	µmol/l	3	2.1	2.1
TGP	UI 37°	22	20	20
TGO	UI 37°	34	31	31
LDH	UI 37°	489	511	511
CK	UI 37°	77	86	86



<http://www.ifrance.com/valab/>



Define the patients context

From data to information: how to define the context?

Goldschmidt, Lent, Chemometrics and Intelligent Laboratory Systems
Volume 28, Issue 1, April 1995, Pages 181-192

Context is defined as the patient-specific data and the physician's hypothesis to be tested concerning the patients' medical problem.

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management
NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Define the patients context

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The better the data fit the context the greater their involvement and impact on the decision to take medical action. This leads to **the concept of context-fit values (CFV's)** for laboratory data.

Depending on the reason for which testing is being requested (**monitoring, screening, or diagnosis**), this concept enables the supplier of data, with the cooperation of the requestor, to analyze how well the data fit in the context frame of the decision maker.

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management
NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Customer awareness

Clinical Diagnostics—Just What the Doctor Ordered? Progress Since the 1800s

By Christopher P. Price

THE USE of chemical methods to aid the diagnosis of disease may date back as far as the sixteenth century. At this time, the doctor performed simple tests, usually on urine, at the patient's bedside. The concept of a laboratory offering a variety of tests was born in the mid-1800s, although ward side room testing was known earlier in the century: a small side room attached to the clinical ward at Guy's Hospital was used for performing tests. It is recorded that independent laboratories were set up in hospitals in Berlin, Wurtzburg, and Vienna between 1840 and 1850. It was probably only in the early part of the twentieth century that pathology laboratories became established and, furthermore, that different disciplines were recognized within the umbrella of pathology. In 1906, Hopkins (1) recognized the importance of chemical pathology as a scientific discipline in medical practice.

Throughout the twentieth century the vast development in clinical laboratory practice has been reflected in the variety of different tests that have been developed, the number of specimens handled by laboratories, and the variety and sophistication of equipment and reagents that are used (Table 1).

Evolution of analytical equipment

Early diagnostic tests were performed with simple reagents, and any color change evaluated with the naked eye; use was also made of gasometric, gravimetric, and titrimetric techniques. Much of the equipment involved complicated glassware, although by modern standards, it now

appears to be very simple in design—particularly early colorimeters. The first quarter of the twentieth century saw the development of separation techniques including electrophoresis, chromatography, and ultracentrifugation.

Much of the analytical work performed in laboratories was undertaken using manual techniques up to the middle of this century. The first automated analytical system was the Auto Analyzer (Technicon Instruments Corp., Tarrytown, New York, U.S.A.) based on the principle of continuous flow fluids, coupled with colorimetry. The key features of early models included continuous dialysis, bubbles in the liquid stream to aid mixing and maintain sample integrity, and a flow-through photometric cell (2). Individual channels were subsequently combined to produce a multiple sequential analyzer (leading to the SMA series, Technicon Instruments Corp.).

The continuous flow analyzer has been extremely successful, with the ability to provide a battery of tests with a high throughput of samples. The major alternatives to this approach, handling large numbers of samples, have been based on analyses being undertaken in organized arrays of

Equipment	Year	Reagents	Year
Colorimeter	1954	Glucose oxidase	1958
Auto analyzer	1957	Radioimmunoassay	1960
Centrifuge analyzer	1959	Heterogeneous immunoassay	1971
Thin film technology	1978	Monoclonal antibodies	1975
Discretionary analyzer	1981	Luminescence immunoassay	1982
Biosensor	1986	DNA probes	1986
Fibrotics	1987	Chimeric antibodies	1987

Professor Price is with the Dept. of Clinical Biochemistry, The London Hospital Medical College, London, England. This paper is based on a presentation given to a symposium on Trends in Diagnostic Testing at Churchill College Cambridge.

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Taking over the doctors' work ?!

The collage includes three articles:

- Who is afraid of the system? Doctors' attitude towards diagnostic systems** by Jacobus Ridderikhoff*, Bart van Herk. *Journal of Medical Informatics* 33 (1999) 91-100.
- Application of the EXPERT Consultation System to Accelerated Laboratory Testing and Interpretation** by Frederick Van Lente, William Castellani, David Chou, Richard N. Matzen, and Robert S. Galen. *CLIN. CHEM.* 32(8), 1719-1725 (1998).
- Medical Informatics** (partial title visible).

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



The patient in the lead: all involved



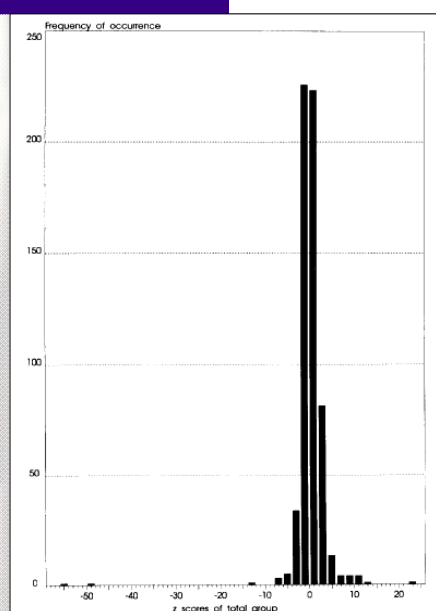
- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



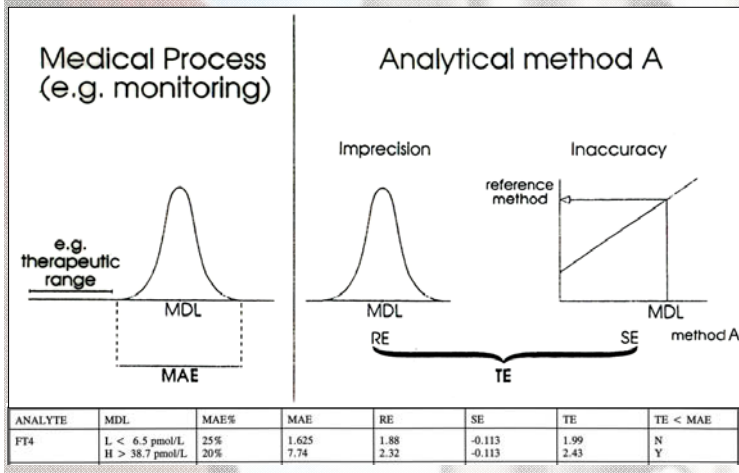
The guessing experiment

Histogram of 611 Z-scores of clinical test results of 3 outpatient clinics and 4 physicians. The Z-scores are the context fits a particular clinical chemical test result.

In:
Chemometrics and Intelligent Laboratory Systems 28 (1995) 181-192 From data to information: how to define the context?
H.M.J. Goldschmidt and R.W. Lent.



Total Error Concept

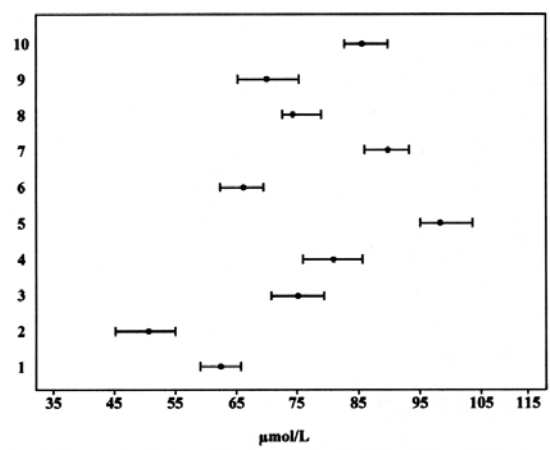


ANALYTE	MDL	MAE%	MAE	RE	SE	TE	TE < MAE
FT4	L < 6.5 pmol/L	25%	1.625	1.88	-0.113	1.99	N
	H > 38.7 pmol/L	20%	7.74	2.32	-0.113	2.43	Y

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Biological variation



Mean Values and Absolute Ranges of Serum Creatinine in Four Samples Taken from Each of 10 Apparently Healthy Women

The age and sex matched reference interval for women aged 18–55 years is 50–100 µmol/L (note that this is not the same as the reference interval for men, even though the groups are in the same age range).

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Biological variation



Desirable Specifications for Total Error, Imprecision, and Bias, derived from intra- and inter-individual biologic variation

Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress." Scand J Clin Lab Invest 1999;59:491-500.

CVw = within-subject biologic variation
 CVg = between-subject biologic variation

I = desirable specification for imprecision
 B = desirable specification for inaccuracy
 TE = desirable specification for allowable total error

	Analyte	Biological Variation		Desirable specification		
		CVw	CVg	I(%)	B(%)	TE(%)
S-	Glucose	5.7	6.9	2.9	2.2	6.9

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Critical difference Reference Change Value



Calculation of RCV We can calculate reference change values using this formula:

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

1st value = 6.60 mmol/L
 2nd value = 5.82 mmol/L
 Change = 6.60 - 5.82 = 0.78 mmol/L
 which is equivalent to (0.78/6.60) * 100 = 11.8%

Now

$$2^{1/2} = 1.414$$

and, as we have seen, CV_A is found from the internal quality control run in the laboratory and was 1.6%, and CV_I is found from the latest published database and is 6.0%.

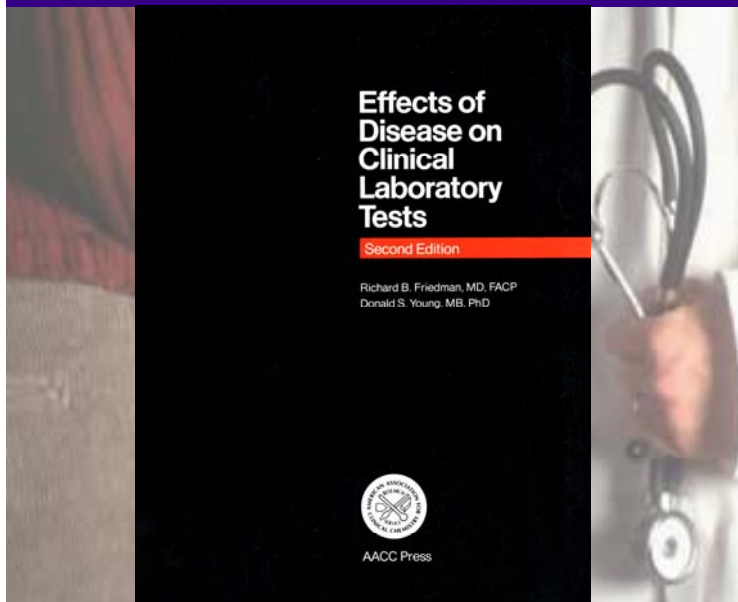
$$\text{Thus } Z = 11.8 / [2^{1/2} * (1.6^2 + 6.0^2)^{1/2}] = 1.35$$

and, looking at the statistical tables, we find that, for that value of Z, the probability that this change is significant is actually quite high: 82%.

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



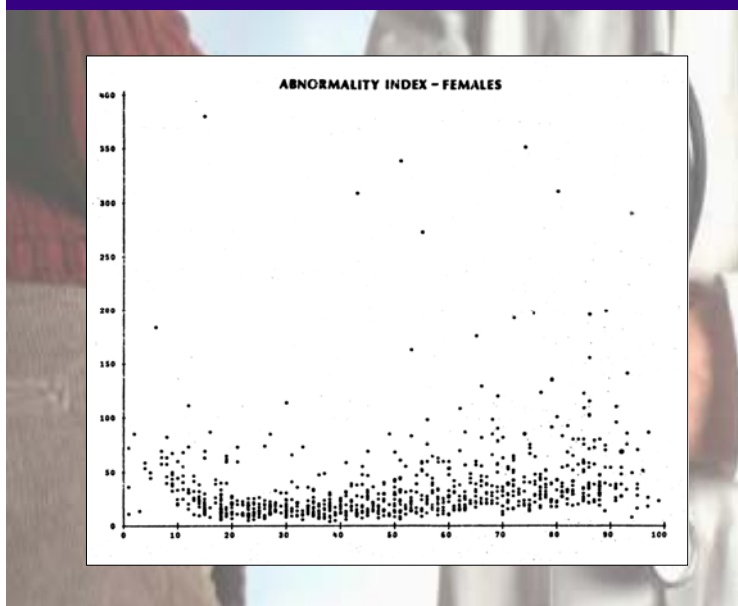
Variation through disease state and medication



- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Age and time dependencies

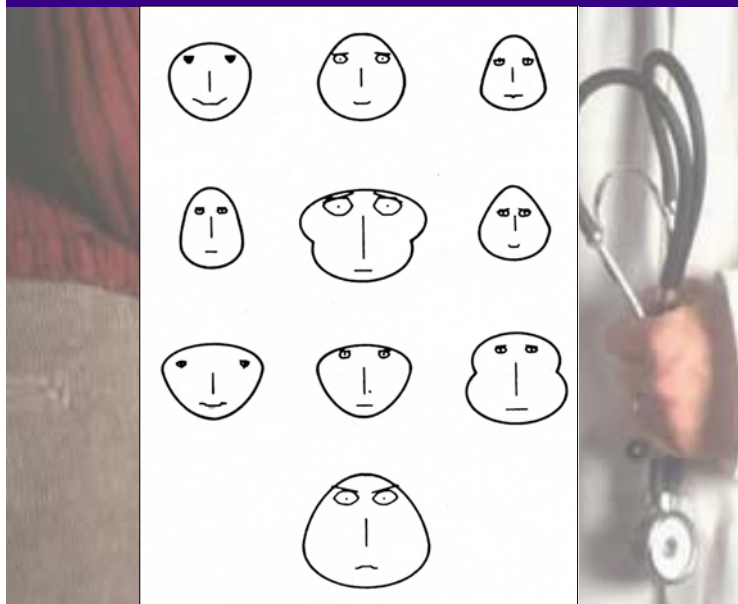


- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Biochemical Individuality and the recognition of personal profiles with a computer.

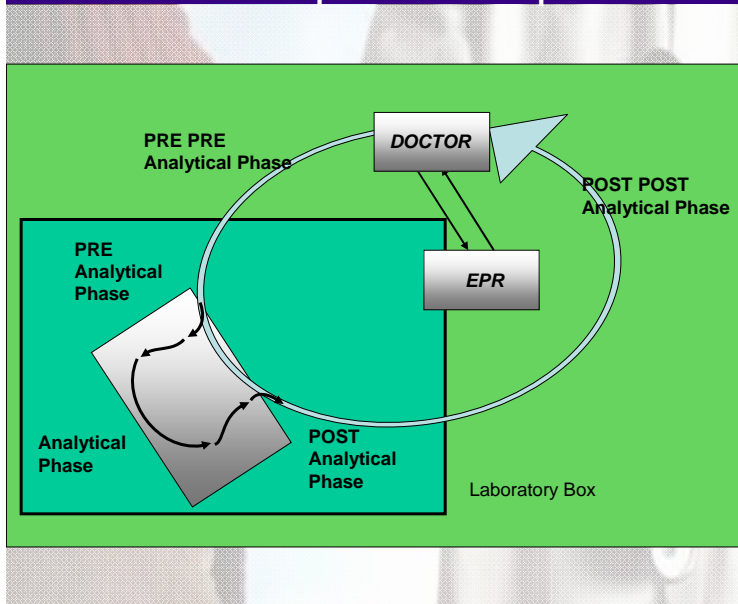
Robertson, et al, Clin. Chem. 26, 30-6, 1980



- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ **Medical concepts**
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ Conclusions



Complete Diagnostic / Therapeutic Loop



- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ **Error management NEXUS**
- ↳ (Analytical) goals
- ↳ Conclusions



Linking the concepts of biological variation and medical allowable error

Table: Calculated and studied error rates

Phase	frequency of occurrence	justification source
Pre-pre-analytical phase	1:8 12.0 %	own enquiry ¹
Pre-analytical phase	1:49 2.0 %	literature
Analytical phase	1:625 0.2 %	results lab author 1 ²
Post-analytical phase	1:45 2.2 %	literature
Post-post-analytical phase	1:19 5.0 %	own enquiry ³
Overall error rate	20.0 %	see paper for calculation
Error budget that can be afforded	26.9 %	see paper for estimation

1 Interviewing clinicians, checking for errors in e.g. thinking wrong hypothesis

2 Internal, not external, quality control figure

3 Interviewing clinicians, checking for e.g. misinterpretation of results

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ **Error management NEXUS**
- ↳ (Analytical) goals
- ↳ Conclusions



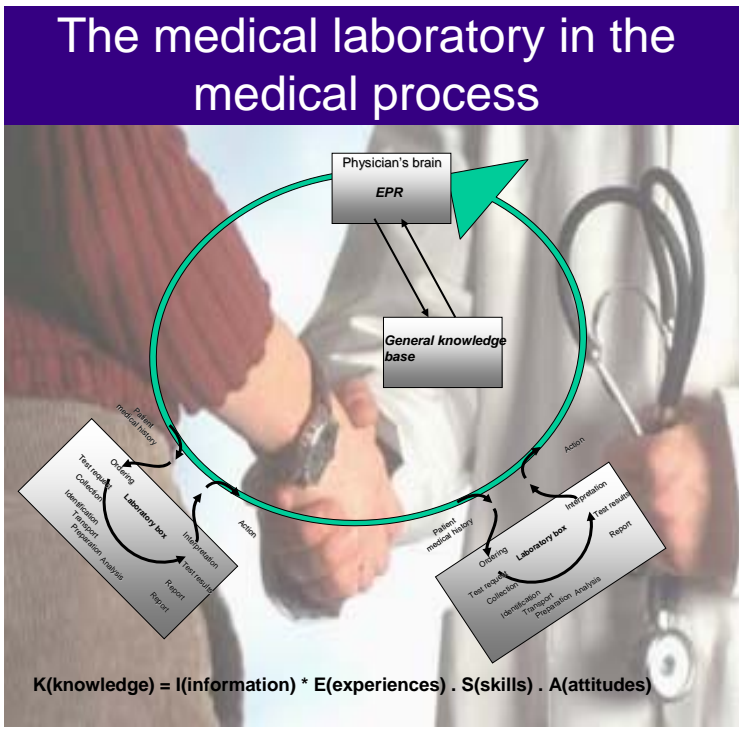
Linking the concepts of biological variation and medical allowable error

In a way the two approaches are: what is right now practically achievable and what is, from a theoretical point of view, possible.

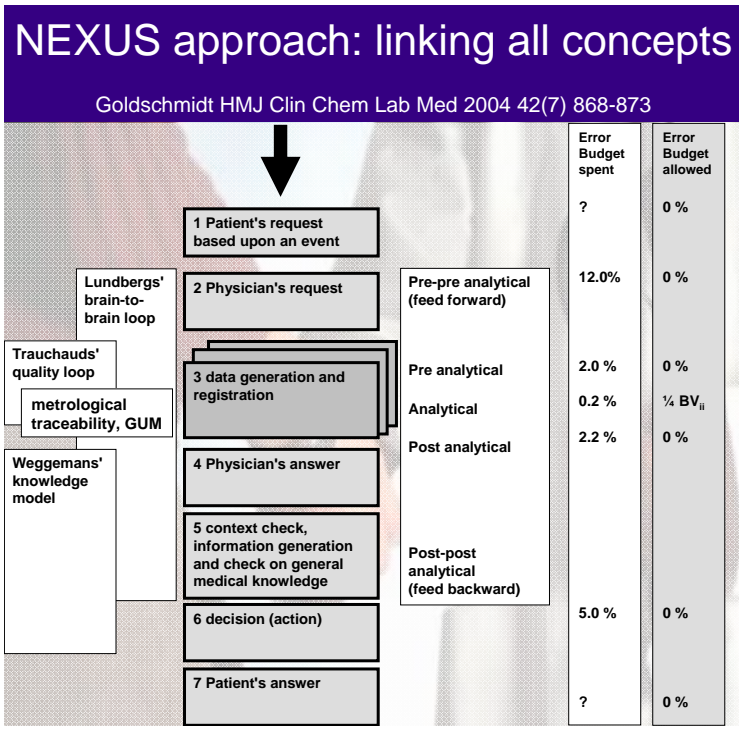
So the potential of laboratory medicine is given by the biological variance concept.

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ **Error management NEXUS**
- ↳ (Analytical) goals
- ↳ Conclusions





Goldschmidt HMJ
 Postanalytical factors and their influence on analytical quality specifications.
 Scand J Clin Lab Invest 1999; 59: 551-554



NEXUS approach

Goldschmidt HMJ Clin Chem Lab Med 2004 42(7) 868-873

In the pre-preanalytical phase (overlapping with laboratory preanalytical phase) to obtain quality the following criteria should be fulfilled:

- full description of patients' context
- balance with other diagnostic tools
- double check on request (by colleague, by software)

100% context fit,
0 % errors

With regard to the laboratory:

- in the preanalytical phase zero errors are allowed,

0 %

- in the analytical phase: traceability should be installed, zero bias and no random error exceeding 1/4 of the intra-individual variation. An QS should be installed

1/4 intra individual biological variation¹

- in the postanalytical phase zero errors are allowed,

0 %

The post-postanalytical phase (overlapping with laboratory postanalytical phase) should live up to the following criteria:

100% context fit,
0 % errors

- full description of new patients' context, based upon all diagnostic information gathered
- overview present of various interpretations and there consequences
- awareness of possible protocols applicable
- double check on interpretation and action (by colleague, by software)

Total error budget

¹ at a specific concentration level

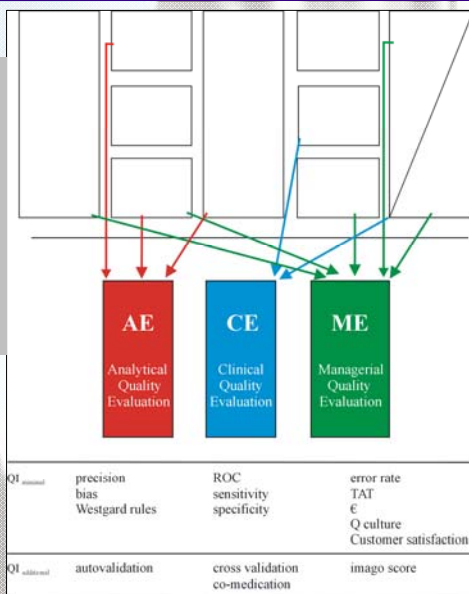
1/4 intra individual biological variation¹

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ **Error management NEXUS**
- ↳ (Analytical) goals
- ↳ Conclusions



Transformation from EFQM into LMQM

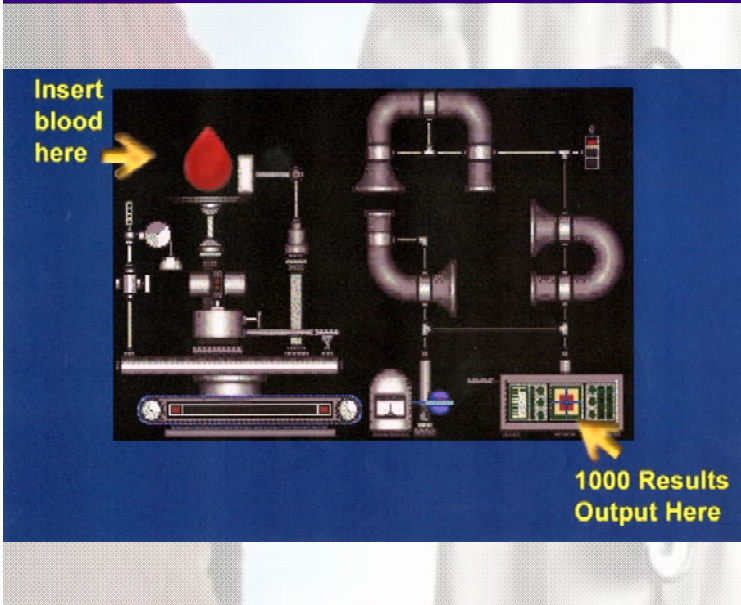
"THE 2011 ANTWERP MEETING"
 28th and 29th March 2011
 QUALITY INDICATORS



- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ **(Analytical) goals**
- ↳ Conclusions



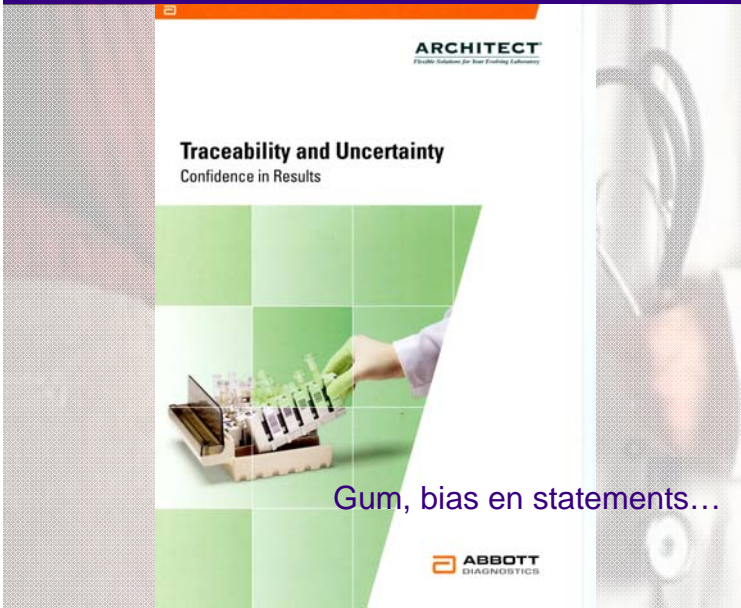
Ideal Laboratory Analyzer



- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ **(Analytical) goals**
- ↳ Conclusions



Relevant for the doctor ?



- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ **(Analytical) goals**
- ↳ Conclusions



Quality of laboratory information

Antwerp versus Stockholm

The Stockholm statements:

1999 quality of laboratory results

The Antwerp statements:

2003 quality of laboratory information

Jean-Claude Libeer formulated the following questions:

Is our information useful for patient care?

Do we know what clinicians want?

Do clinicians know what we can offer?

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ **Conclusions**

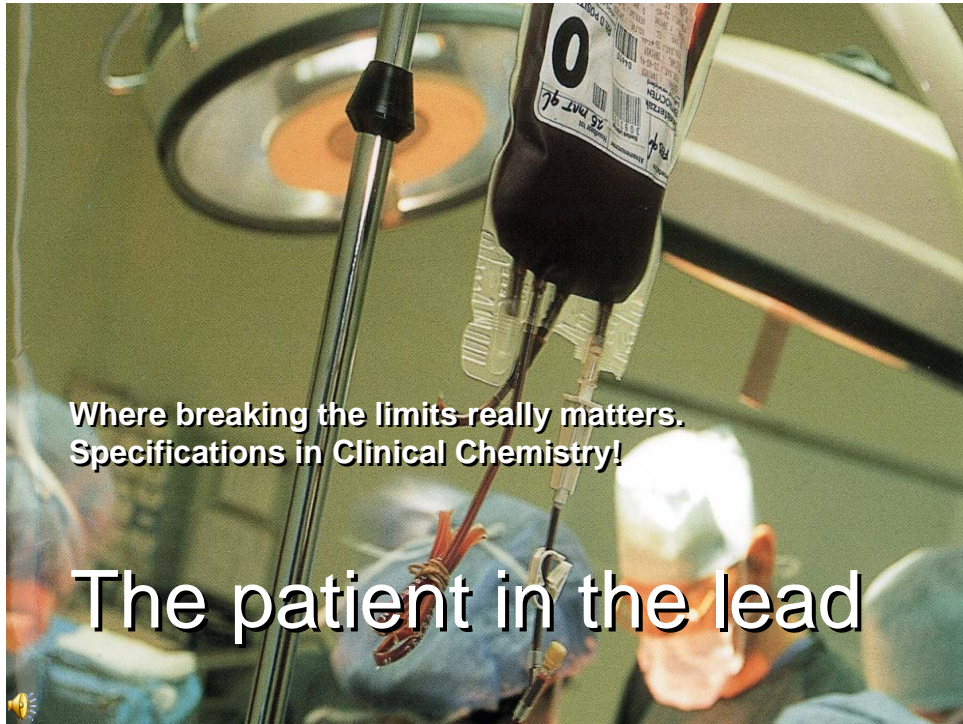


Define *personalized* analytical specifications

- It's time to recognize the physician as well as the patient
- Use comprehensive models
- Use time dependencies
- Use autovalidation and autoverification
- Consultation
- Bring the quality upto the new level:
 - systematic errors: zero
 - random errors: $\frac{1}{4} BV_{ij}$

- ↳ Introduction
- ↳ Brain-to-brain info loop
- ↳ Medical concepts
- ↳ Error management NEXUS
- ↳ (Analytical) goals
- ↳ **Conclusions**





Where breaking the limits really matters.
Specifications in Clinical Chemistry!

The patient in the lead