

A photograph of two people climbing a steep, snow-covered mountain. The person in the foreground is wearing an orange jacket and dark pants, while the person further up is wearing a red jacket. They are using ropes and ice axes. The sky is blue with scattered white clouds.

Quality Specifications

Berlin 2009

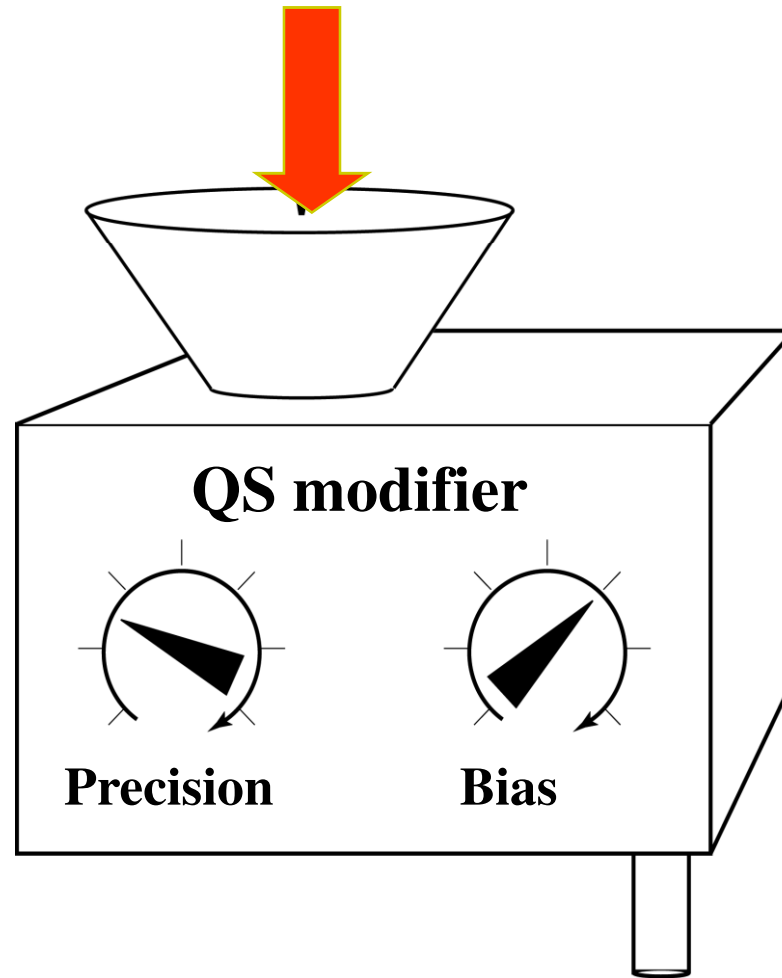
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WHY?

To know the (analytical) quality is necessary for correct interpretation of laboratory tests.

To be able to optimize interpretation of laboratory tests, quality specifications are necessary

Quality specifications



Quality control rules
Diagnostic accuracy

What will I talk about?

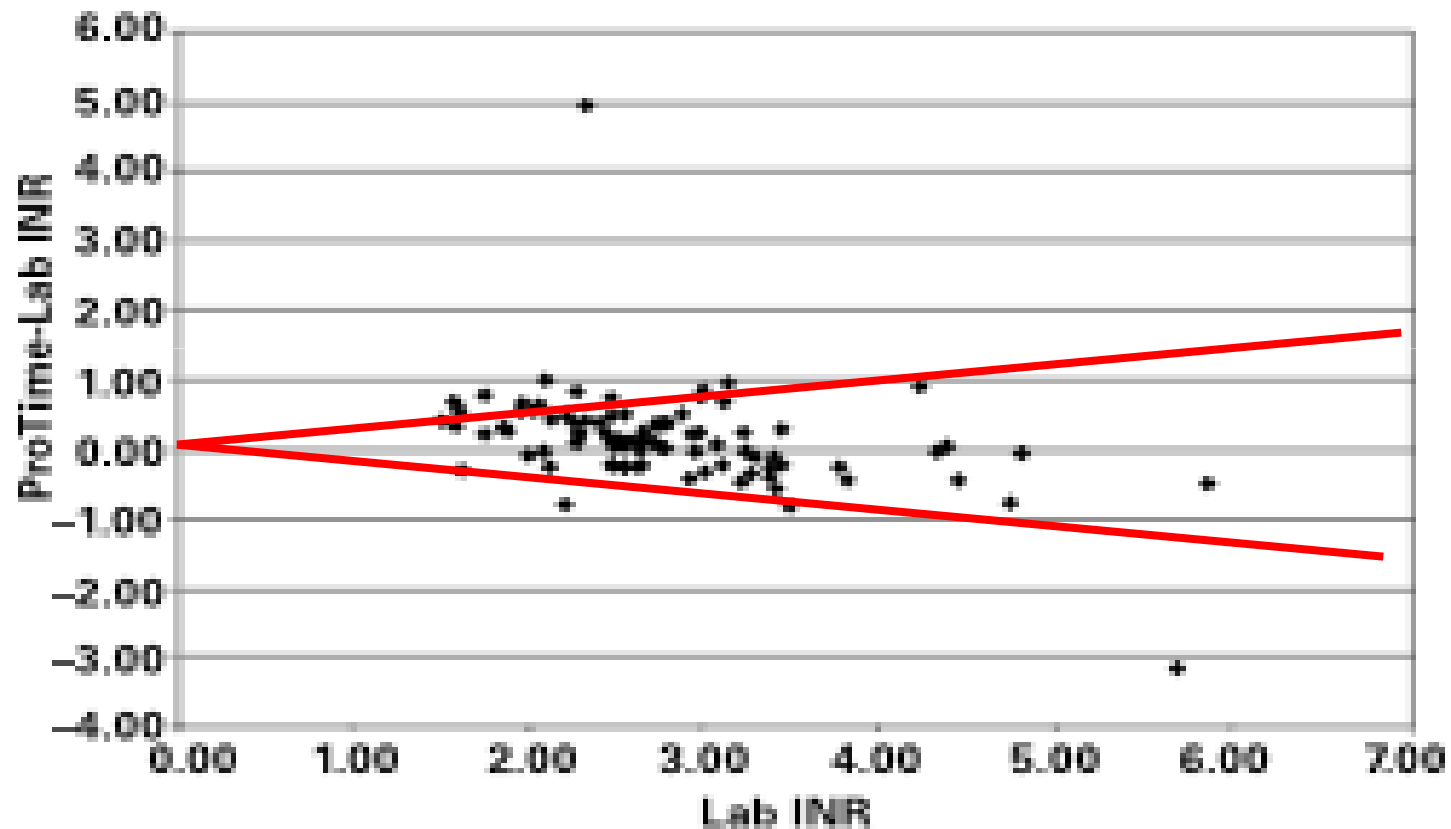
- **One statement and two questions**
- **Is it OK to use within subject variation as a basis for quality specifications?**
- **What about the “clinical” approach – is it possible?**
- **Is it advisable to write clinical guidelines without quality specifications?**

**As important as quality specifications
for the analytical part is
quality specifications for the
pre-analytical and
post-analytical face**

Why are quality specifications always given in percentages?

- **It assumes that the error always is proportional**
- **It is easier in EQAS to fulfil criteria in the high level than in the low level.**

Patient self-testing: Difference between ProTime and laboratory INR vs laboratory INR.



Are QS – evidence based?

Has it been shown that certain QS will improve the outcome of patient handling better than others?

Or

Are the quality of medical laboratories depending on what quality specifications we set in external quality assessment schemes.

Setting quality goals to optimize interpretation of laboratory results

Two principally different approaches:

To minimize the effect of analytical uncertainty compared to uncertainties that we can not influence (e.g. within-subject biological variation)

To be able to minimize the effect of false diagnostic classifications or false actions in monitoring situations

Within-subject biological variation

This is done because we want the analytical variation not to influence the total variation. It has nothing to do with clinical needs. Usually it is argued that the imprecision should be $< \frac{1}{2}$ the within-subject biological variation, and it then accounts for about 12 % of the total variation.

Some concerns with within-subject variation as a basis for Qs

Often other “biological” sources for variation is not taken into account e.g.– posture, food, exercise, diseases, within-day biological variation.

The way to calculate within-subject variation is not done in a standardized way.

Confidence intervals are not usually given.

Example: U- albumin

To find the within-subject biological variation for u-albumin, a systematic search was done for papers on biological variation.

More than 30 papers were found through more than 20 years

Current Issues in Measurement and Reporting of Urinary Albumin Excretion

W. Greg Miller,^{1*} David E. Bruns,² Glen L. Hortin,³ Sverre Sandberg,⁴ Kristin M. Aakre,⁴ Matthew J. McQueen,⁵ Yoshihisa Itoh,⁶ John C. Lieske,⁷ David W. Secombe,⁸ Graham Jones,⁹ David M. Bunk,¹⁰ Gary C. Curhan,¹¹ and Andrew S. Narva,¹² on behalf of the National Kidney Disease Education Program–IFCC Working Group on Standardization of Albumin in Urine

BACKGROUND: Urinary excretion of albumin indicates kidney damage and is recognized as a risk factor for

urine. The recommended reference intervals for the ACR do not take into account the large interperson dif

Table S1. Summary of studies related to evaluation of intra-individual biological variability for urine albumin and albumin/creatinine ratio (a, b).

Ref	N	Type of patients	Albumin concentration (c)	Time interval between samples	Number of samples	Type of urine collection	Storage temperature °C	Intraindividual biological variation (CVi, %)				C
								Albumin Concentration	Albumin in 24 hours excretion	Albumin Excretion Rate	Albumin/Creatinine Ratio	
1	20	Healthy	34 mg/24 hours	4 hours	6	4 hour timed	4 or frozen for 14 days			80	52	
2	5	Mild HT or healthy	30 µg/min	12 hours	7	Timed overnight and day	-70	58		60	52	
2	25	Mild HT or healthy	4 µg/min	12 hours	7	Timed overnight and day	-70	51		48	34	
3	32	Diabetes 1	24 mg/L (range 8,2-86)	day	2	24 h	-20		41			
4	60	Healthy	8.0 mg/24h	day	3	24 h	-20		44			
4	60	Healthy	6.6 µg/min	day	3	Daytime (08-23)	-20			50		
4	60	Healthy	4.2 µg / min	day	3	Overnight (23-08)	-20			58		
4	135	Diabetes	8,6 mg/24h	day	3	24 h	-20		35			
4	63	Diabetes	84,9 mg/24 h	day	3	24 h	-20		37			
4	14	Diabetes	458,5 mg/24 h	day	3	24 h	-20		47			
5	31	Healthy	not stated	day	5	Second morning	Fresh	29			22	
6	334	Diabetes 1	10% >3 mg /mmol; 90% <3 mg/mmol	day	3	First morning	?	60			49	
7	8	Diabetes	MA	day	3	Timed overnight	-20			19		
7	8	Diabetes	MA	day	3	24 h	-20		14			
7	8	Diabetes	MA	day	3	Random spot sample	-20				34	
8	201	Healthy	0,1-122 mg/L	day	2	First morning	-20	27				
8	16	Healthy	1,2-7,4 µg/min	day	3	Timed overnight	-20			23		
9	7	Healthy	not stated	day	4	Second morning	Fresh				69	
						Timed overnight and early morning						
10	8	Diabetes 1	Normoalbuminuria	day	7	early morning	-20			9 to 63	17 to 32	
11	17	Diabetes 2	Normoalbuminuria	day	3	Timed overnight	-70			36	28	
11	64	Diabetes 2	Microalbuminuria	day	3	Timed overnight	-70			25	11	
11	6	Diabetes 2	Macroalbuminuria	day	3	Timed overnight	-70			22	4	
12	216	High-normal or MA	22,5 (8,6-125,7) mg/24 h	day	2	24 h	Fresh	19	14		14	
13	21	Diabetes, Children	8,5 mg/g and 11 mg/L	day ?	3	First morning	3 days, room temp	89			61	
13	10	Healthy, Children	4,7 mg/g and 5,8 mg/L	day ?	3	First morning	3 days, room temp	33			19	
13	10	Healthy, adults	5,9 mg/g and 7,7 mg/L	day ?	3	First morning	3 days, room temp	25			26	
14	11	Healthy	7,8 mg/24 h	<week	5	24 h	-20	61	70		85	
14	11	Healthy	0,58 mg/mmol creatinine	<week	10	First morning	-20	36			31	
14	11	Healthy	1,1 mg/mmol creatinine	<week	10	Random untimed	-20	86			103	
14	16	Diabetes	1,3 mg/mmol creatinine	<week	10	First morning	-20	61			39	
15	8	Healthy	1,7-10,2 µg/min	week	5	Timed overnight	-20			36	33	
15	15	Diabetes	1,9-26 µg/min	week	5	Timed overnight	-20			38	34	
15	12	Diabetes	31-123 µg/min	week	5	Timed overnight	-20			40	43	
16	4678	Random selection	<1 mg/L and all participants	3-6 weeks	2	24 h	-20	46	49		49	
16	1933	Random selection	> 1.0 mg /L	3-6 weeks	2	24 h	-20	27	29		29	
16	1709	Random selection	AE < 30 mg/24h and > 1mg/L	3-6 weeks	2	24h	-20	25	29,0		28,0	
16	204	Random selection	30-299 mg/24 h	3-6 weeks	2	24 h	-20	M/W=42/78	M/W=39/78		M/W=39/81	
3	32	Diabetes	24 mg/L (range 8,2-86)	month		24 h	-20		52			

U- albumin

some variation in the papers found

- **Sampling time (morning, overnight, spot etc)**
- **Reporting units (A/L, A excr/24 h, A/C ratio)**
- **Length of study (Within day, Between Days, weeks, months)**
- **Concentrations (low / medium / high)**
- **Type of persons (diseased / healthy)**

U-albumin – analytical issues

- **Collection tubes – absorption of albumin to the tube walls**
- **Storage before analyzing, room, freezer (-20 or -80 degrees)**
- **Consecutive analyzing or analyzing after storage in the same series or in different series**

Large variation in results

- **CV variation from 11% (4) to 106% in the albumin / creatinine ratio**
- **Conclusions: It is a need for standardization**

WG in EFCC (chair Bill Bartlett, UK)

Terms of references:

- 1. To describe and characterize papers on biological variation for one or two constituents. Sources for variation in papers on estimation of biological variation in the papers should be identified.**
- 2. To develop a critical appraisal check list for papers on biological variation.**
- 3. To develop a method for meta-analysis of data on within-subject variation.**

Clinical approach

Consequences of false classifications

- **Minimize the number of false positives and false negatives –**
- **Give weight (medical and/or economical) to the different classifications.**

This has been dealt with in the previous lecture

Opinions of clinicians and patients

A method to discover how the clinicians are using the tests.

It is then possible to extract what analytical quality they presuppose that they have.

This can then be used (a) for quality specifications or (b) to educate physicians in how they should interpret the results.

How to find the "opinions" of the clinicians ?

1. *To examine the journals to see what the physicians do in the real life situation*
2. *To distribute case histories to simulate real life*

Post-analytical external quality assurance (P-EQAS)

Distribution of case-histories in which the laboratory result is of great importance. We then incorporate these questions in a larger questionnaire to evaluate post-analytical performance (how do they handle the result)

Example

Clinical Chemistry 52:10
1871–1878 (2006)

Evidence-Based
Laboratory Medicine
and Test Utilization

Postanalytical External Quality Assessment of Warfarin Monitoring in Primary Healthcare

ANN-HELEN KRISTOFFERSEN,^{1*} GEIR THUE,² and SVERRE SANDBERG^{1,2}

Two case histories

Circulated to 3781 GPs

Patient A: Aortic stenosis with mechanical heart valve prosthesis Stable INR results of about INR 3.3

Patient A: Mechanical heart valve prosthesis

Last months stable INR results (3.0-3.5)

Last result: INR 3.3

How low should the next INR result be for you to increase the marevan dose: _____

How high should the next INR result be for you to reduce the Marevan dose? _____

Critical difference

The differences between the two results given is the medical critical difference (CD) which one should be able to detect by the actual measurement method.

Dependent on the question, the CD can comprise:

- pre-analytical variation**
- imprecision under defined reproducibility conditions**
- within-subject variation**
- bias**

Calculations

$$CD = bias + z \cdot \sqrt{2} \cdot \sqrt{CV_{ws}^2 + CV_a^2}$$

$$CV_a = \sqrt{((CD - bias) / z \cdot \sqrt{2})^2 - CV_{ws}^2}$$

Critical difference

	Increase in dose from INR 3.3
Median INR value 10/90 perc	2.6 (2.9 / 2.0)
Critical difference	24%
CVa	4.1

Feedback report to the participants

- **Information on**

Own results compared to others

Corresponding analytical quality

**Information on analytical and biological
variation**

Guidelines for use of the actual laboratory tests

Postanalytical External Quality Assessment of Urine Albumin in Primary Health Care: An International Survey

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Mathias Müller,⁴ Marijana V. Lovrencic,⁵ Inger Plum,⁶ Kaja Kallion,⁷ Alar Aab,⁸ Marge Kutt,⁹
Philippe Gillery,¹⁰ Nathalie Schneider,¹⁰ Andrea R. Horvath,¹¹ Rita Onody,¹¹ Wytze Oosterhuis,¹²
Carmen Ricos,¹³ Carmen Perich,¹⁴ Gunnar Nordin,¹⁵ and Sverre Sandberg^{1,2}

Quality specifications set by GPs and patients

Constituent	Quality specification CVa	Ref	Comment
Hb	2.8 %	<i>SJCLI. 1991;51:453</i>	2.3 – 7.8
SR	10 mm	<i>SJCLI. 1994;54:291</i>	
HbA1c - GPs	1-3%	<i>Clin Chem. 2005;51:1145</i>	
HbA1c - patients	3%	<i>Clin Chem. 2001;47:1212</i>	
Glucose GPs	3%	<i>Clin Chem. 2005;51:1145</i>	
Glucose pat. norm	7%	<i>Clin Chem. 2001;47:67</i>	
Glucose pat. hypo	3%	<i>Clin Chem. 2001;47:67</i>	
PT-INR	15%	<i>Clin Chem. 2006;52:1871</i>	CD=8%
U-albumin	14%	<i>Clin Chem. 2008;54:1630</i>	CD=33%

Professional recommendations

- often done by organisation and implemented in recommendations**

- **Often use of the GOBSAT methodology
(good old boys sat at a table)**
- **Typical examples are ADA guidelines for
glucose and HbA1c**

*The National Collaborating Centre
for Chronic Conditions*

Funded to produce guidelines for the NHS by NICE

TYPE 2 DIABETES

National clinical guideline for management
in primary and secondary care (update)

Measure HbA_{1c} using high-precision methods and report results in units aligned with those used in DCCT Trial (or as recommended by national agreement after publication of this guideline).²¹⁸

International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes

THE INTERNATIONAL EXPERT COMMITTEE*

An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes in individuals with

type 2 diabetes has a more gradual onset, with slowly rising glucose levels over time, and its diagnosis has required specified glucose values to distinguish pathologic glucose concentrations from the distribution of glucose concentrations in

relied on distributions of glucose levels, rather than on the relationship of glucose levels with complications, to diagnose diabetes despite emerging evidence that the microvascular complications of diabetes were associated with a higher range of fasting and OGTT glucose values (11,13–15). The diagnostic glucose values chosen were based on their association with decompensation to “overt” or symptomatic

Recommendations A1c

Table 2—*Recommendation of the International Expert Committee*

For the diagnosis of diabetes:

- The A1C assay is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications.
- The A1C assay has several advantages over laboratory measures of glucose.
- Diabetes should be diagnosed when A1C is $\geq 6.5\%$. Diagnosis should be confirmed with a repeat A1C test. Confirmation is not required in symptomatic subjects with plasma glucose levels >200 mg/dl (>11.1 mmol/l).
- If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.
- A1C testing is indicated in children in whom diabetes is suspected but the classic symptoms and a casual plasma glucose >200 mg/dl (>11.1 mmol/l) are not found.

EFCC - WG for guidelines

- ***Terms of reference:***

- -

- -

- **Co-operate with clinical guidelines developers (e.g. SIGN, ADA, NICE) for the development of the laboratory part of clinical guidelines.**

Summary

- **Quality specifications are important but may be difficult to set.**
- **All current methods – biological variation, clinical reasoning and professional recommendations have serious limitations**
- **Why are Qs always given in % and not in e.g. absolute values together with percentages**

- **QSSs for the pre- and postanalytical face should be more emphasized**
- **The effect of using different quality specifications should be studied**
- **Laboratory people should be more involved in the writing of quality specifications for important constituents in clinical guidelines**

There is still a way to go

Thank you

references

- 1. Aakre KM, Thue G, Subramaniam-Haavik S, et al. Postanalytical External Quality Assessment of Urine Albumin in Primary Health Care: An International Survey. *Clin Chem.* 2008;54:1630-1636.
- 1. Kristoffersen AH, Thue G, Sandberg S. Postanalytical external quality assessment of warfarin monitoring in primary healthcare. *Clin Chem.* 2006;52:1871-1878.
- 1. Skeie S, Perich C, Ricos C, et al. Postanalytical external quality assessment of blood glucose and hemoglobin A1c: an international survey. *Clin Chem.* 2005;51:1145-1153.
- 1. Skeie S, Thue G, Sandberg S. Patient-derived quality specifications for instruments used in self-monitoring of blood glucose. *Clin Chem.* 2001;47:67-73.
- 1. Skeie S, Thue G, Sandberg S. Interpretation of hemoglobin A(1c) (HbA(1c)) values among diabetic patients: implications for quality specifications for HbA(1c). *Clin Chem.* 2001;47:1212-1217.
- 1. Thue G, Sandberg S, Fugelli P. Clinical assessment of hemoglobin values by general practitioners related to analytical and biological variation. A study based on case stories. *Scand J Clin Lab Invest.* 1991;51:453-459.
- 1. Thue G, Sandberg S, Fugelli P. The erythrocyte sedimentation rate in general practice: Clinical assessment based on case histories. *Scand J Clin Lab Invest.* 1994;54:291-300.

Case History

A 57 year old male taxi-driver, diagnosed two years ago with type 2 diabetes is in your office for a scheduled consultation. He is on oral antidiabetic treatment. He has been overweight for several years, has stopped smoking and has begun a modest exercise programme. He has no diabetes-related complications, and is otherwise healthy. There is no history of early cardiovascular disease in his family. He feels well today.

Today's results are similar to previous consultations: blood pressure 145/90; HbA1c 7.7%, total cholesterol 6.1mmol/L, HDL 1.1mmol/L, LDL 3.9mmol/L, triglycerides 1.6mol/L (fasting). His creatinine level is normal. He weight 99kg; BMI 29 kg/m².

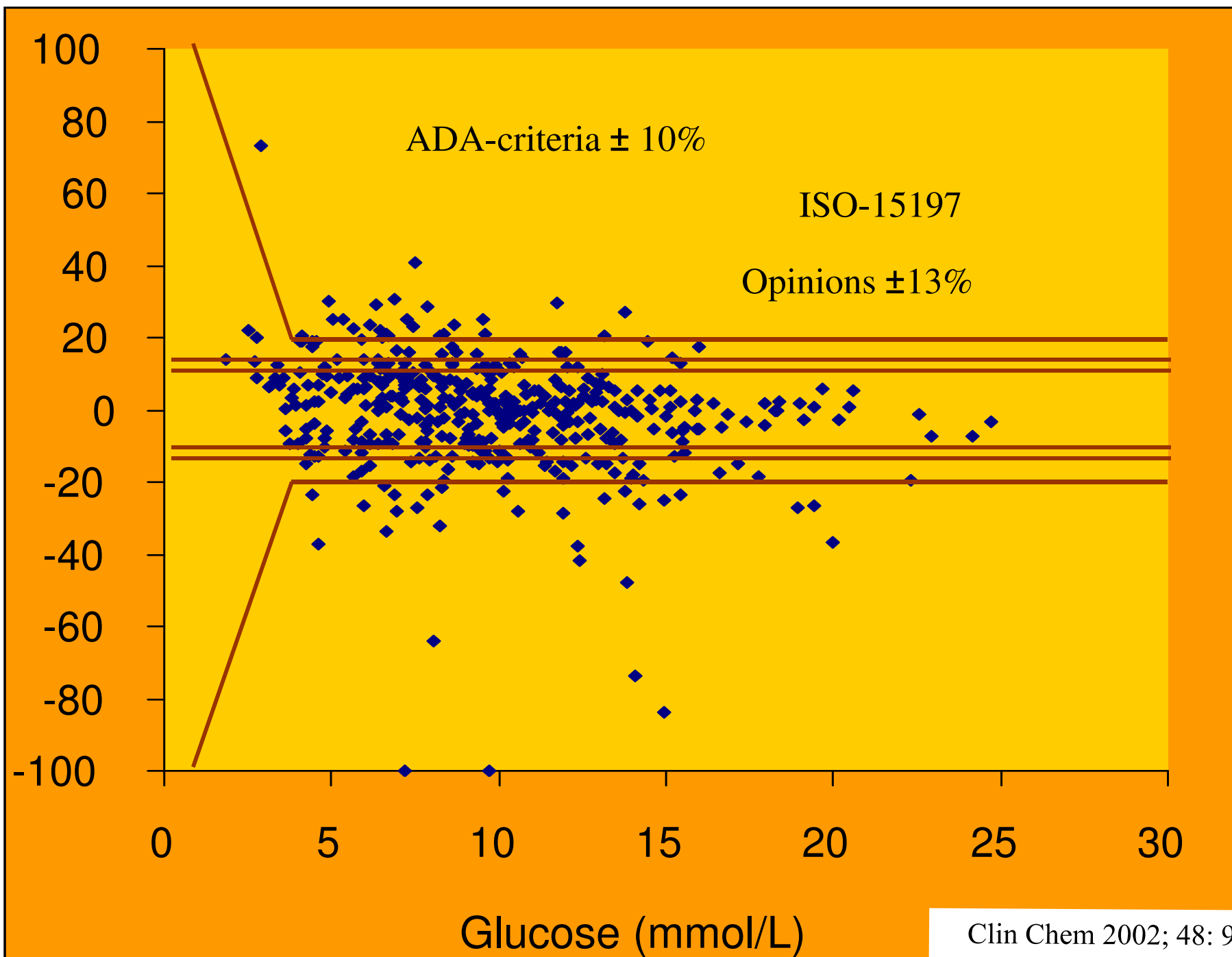
The patient has not been previously tested for microalbuminuria (MA). He delivers a urine sample in accordance with the routines you have stated for first time examination for MA. This urine sample tests negative on an ordinary urine dipstick analysis.

Critical difference

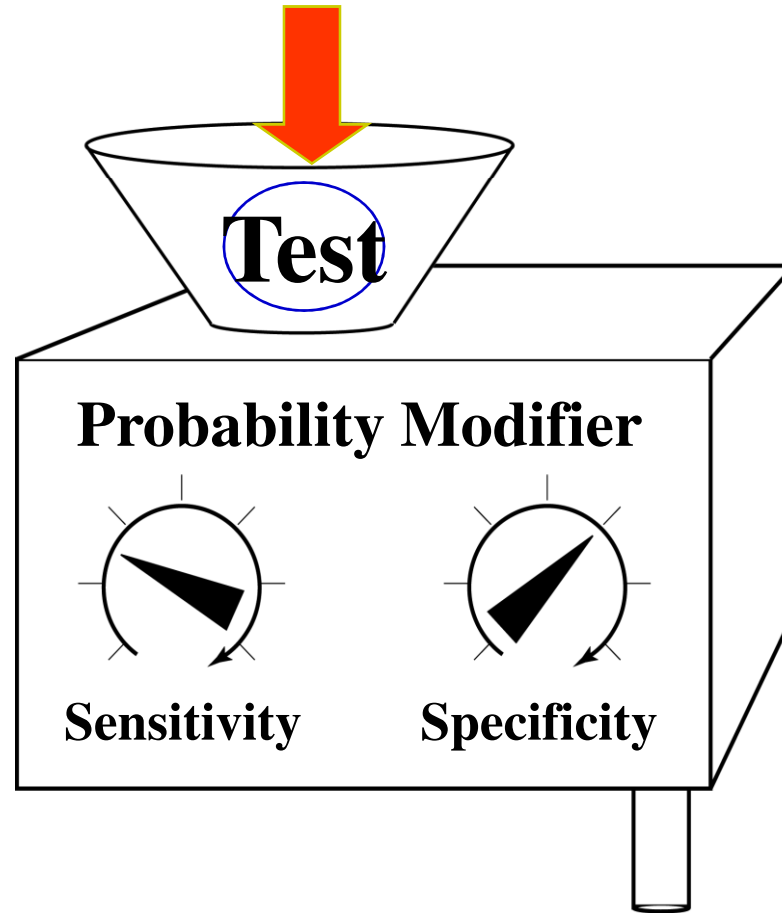
Assume that at today's consultation the taxi-driver has an albumin/creatinine-ratio of 15 mg/mmol (150 mg/mg). A year later the patient provides another urine sample.

Based on the answer you have chosen above, what should the value be to indicate:

- deterioration in MA during the year , i.e. the value should have increased at least to: _____
- improvement in MA during the year, i.e. the value should have decreased at least to: _____



Pre-test probability



Post-test probability
Diagnostic accuracy

NACB guidelines

Clinical Chemistry 48:3
436–472 (2002)

Evidence-based
Laboratory Medicine
and Test Utilization

Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus

DAVID B. SACKS,^{1*} DAVID E. BRUNS,² DAVID E. GOLDSTEIN,³ NOEL K. MACLAREN,⁴
JAY M. McDONALD,^{5,6} and MARIAN PARROTT⁷

Recommendation: Enzymatic methods for glucose analysis are relatively well standardized. Despite the low imprecision at the diagnostic decision limits of 7.0 mmol/L (126 mg/dL) and 11.1 mmol/L (200 mg/dL), classification errors may occur. Because of the relatively large intraindividual biological variability (CVs of ~5–7%), FPG values of 5.8–6.9 mmol/L (105–125 mg/dL) should be repeated and individuals with FPG of 5.3–5.7 mmol/L (96–104 mg/dL) should be considered for follow-up at intervals shorter than the current ADA recommendation of every 3 years.

Level of evidence: E