



Chemical Pathology

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General Serum Chemistry & Therapeutic Drugs Program

REVISION OF ALLOWABLE LIMITS OF PERFORMANCE

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Analytical performance goals have been used in the RCPA/AACB Chemical Pathology QAP since its establishment almost thirty years ago. These goals, called Allowable Limits of Performance (ALP's) were largely a choice between total error goals of $\pm 5\%$, $\pm 10\%$ or $\pm 20\%$. They were initially established and maintained by advisory expert groups based on expert opinion and peer based capability.

In 1999 a meeting was organised at the Nobel Institute in Stockholm by the IFCC and ISO Technical Committee TC212 at which they established a consensus hierarchy of preferred methods for establishing performance goals. In summary those methods were:

1. Goals based on clinical outcome
2. Goals based on clinical decision making
 - a. Clinician survey
 - b. Biological inter and intra individual variability
3. Goals based on Expert Opinion
4. Goals based on peer capability (eg from EQA)
5. Goals otherwise based on state of the art.

From this hierarchy it can be seen that our current ALP's, being based on expert opinion and peer based capability can be improved upon. Whilst goals based on clinical outcome are rare and clinician surveys uncommon, intra-individual and inter-individual biological variability estimates are available for most common analytes.

The AACB's Scientific and Regulatory Affairs Committee established a working party on Allowable Limits of Performance which has presented every year at the QAP update AACB Scientific Conference as well as at the RCPA Pathology Update and AACB Scientific Education Seminars. At these meetings, the feasibility of applying biological variability as the basis for all ALP's was presented.

ALP'S BASED ON BIOLOGICAL VARIABILITY

Biological variability can be considered as either an intra-individual variability (CV_i) or the inter-individual variability (CV_g or group variability). Similarly, analytical goals may relate to monitoring a single patient or making a diagnosis based on the likelihood of belonging to a healthy or diseased group of patients. Generally the more difficult task is to perceive a change within an individual

compared to being able to tell the difference between individuals as the variation in a single person is less than the variation between people.

The analytical goal for monitoring a patient is that noise added by analytical uncertainty should be less than half the daily biological variability of the patient ($CV_a < \frac{1}{2} CV_i$). For some analytes which are tightly controlled by the body (eg sodium and osmolality), most methods cannot achieve this goal and we recognise that for sodium and osmolality, the contribution of analytical 'noise' is greater than the daily variations of an individual patient. Nevertheless this certainly does not mean that our sodium and osmolality measurements are useless, as they can still be used to detect large variations in patients and able to be used to make a diagnoses based on reference limits. The performance goals for diagnosis are wider and typically expressed as Total error (TE) = $0.25 (CV_i^2 + CV_g^2)^{\frac{1}{2}} + 1.65 \times \frac{1}{2} CV_i$.

Callum Fraser also described a fine tuning of imprecision and total error goals from minimal, desirable and optimal. EQA experts have also considered that when stating total error goals for EQA programs, we should be 99% sure when we say that a laboratory has exceeded the performance goals (rather than 95% sure) so 2.33 is used as the multiple for imprecision rather than 1.65.

	Monitoring (ALP = 2 x CV _a)	Diagnosis (ALP = TE)
Optimal	$CV_a = \frac{1}{4} CV_i$	TE = 0.125 $(CV_i^2 + CV_g^2)^{\frac{1}{2}} + 2.33 \times \frac{1}{4} CV_i$.
Desirable	$CV_a = \frac{1}{2} CV_i$	TE = 0.250 $(CV_i^2 + CV_g^2)^{\frac{1}{2}} + 2.33 \times \frac{1}{2} CV_i$.
Minimal	$CV_a = \frac{3}{4} CV_i$	TE = 0.375 $(CV_i^2 + CV_g^2)^{\frac{1}{2}} + 2.33 \times \frac{3}{4} CV_i$.

Therefore the new ALP limits are all defined using biological variability principles but only adopted when the majority of participants can achieve the goals. As a general rule, a goal was adopted if over 80% of laboratories could achieve the performance as we also sought to encourage further refinement of method particularly to achieve the tighter monitoring goals.

THE NEW BIOLOGICAL VARIABILITY BASED ALP'S

Of the 42 analytes reviewed, the ALP for 21 analytes were tightened (50%), 8 were loosened (19%) and 13 remained largely the same (31%). Fixed limits were also standardised at the lower reference or relevant decision limits.

Analyte		Old ALP			New ALP					
		±	To	Then %	±	To	Then %	Comment	Level	Basis
1	T Acid Phos	1.5	10	15%	1.5	10	15%	Same	Desirable	Total Error
2	P Acid Phos	1.5	10	15%	1.5	10	15%	Same	Desirable	Total Error
3	ALT	8	60	15%	5	40	12%	Tighter	Optimal	Imprecision
4	Albumin	2	20	10%	2	33	6%	Tighter	Desirable	Total Error
5	Alk Phos	15	100	15%	15	125	12%	Tighter	Desirable	Total Error
6	Amylase	15	100	15%	10	100	10%	Tighter	Desirable	Imprecision
7	AST	8	60	15%	5	40	12%	Tighter	Desirable	Imprecision
8	Bicarbonate	2	20	10%	2	20	10%	Same	Minimal	Total Error
9	Total Bili	5	50	10%	3	25	12%	Looser	Optimal	Imprecision
Analyte		Old ALP			New ALP					

		±	To	Then %	±	To	Then %	Comment	Level	Basis
10	Conj Bili	10	50	20%	3	15	20%	Same	Optimal	Imprecision
11	Calcium	0.10			0.10	2.50	4%	Same	Minimal	Imprecision
12	Chloride	3			3	100	3%	Same	Minimal	Total Error
13	Cholesterol	0.5	10	5%	0.3	5	6%	Looser	Desirable	Imprecision
14	CK-MB	6	40	15%	3	15	20%	Looser	Desirable	Imprecision
15	Creat Kinase	15	100	15%	15	125	12%	Tighter	Optimal	Imprecision
16	Creatinine	10	100	10%	8	100	8%	Tighter	Minimal	Imprecision
17	Ferritin	6	40	15%	4	27	15%	Same	Desirable	Imprecision
18	Fructosamine	30	300	10%	15	250	6%	Tighter	Minimal	Imprecision
19	GGT	8	60	15%	5	40	12%	Tighter	Desirable	Imprecision
20	Glucose	0.5	5	10%	0.4	5	8%	Tighter	Desirable	Imprecision
21	HDL Chol	0.20	2.00	10%	0.10	0.80	12%	Looser	Minimal	Imprecision
22	Iron	5			3	25	12%	Tighter	Optimal	Imprecision
23	TIBC	10			4	50	8%	Tighter	Minimal	Total Error
24	Lactate	1	10	10%	0.5	4	12%	Looser	Optimal	Imprecision
25	LD	30	200	15%	20	250	8%	Tighter	Desirable	Imprecision
26	Lipase	40	200	20%	12	60	20%	Same	Desirable	Imprecision
27	Magnesium	0.12			0.10	1.25	8%	Tighter	Minimal	Total Error
28	Osmolality	8			8	266	3%	Same	Minimal	Total Error
29	Phosphate	0.10	1.00	10%	0.06	0.75	8%	Tighter	Desirable	Imprecision
30	Potassium	0.2			0.2	4.0	5%	Same	Desirable	Imprecision
31	Protein	5			3	60	5%	Tighter	Desirable	Total Error
32	Sodium	3			3	150	2%	Same	Minimal	Total Error
33	Transferrin	0.50			0.2	2.5	8%	Tighter	Minimal	Total Error
34	Triglyceride	0.2	2	10%	0.2	1.6	12%	Looser	Optimal	Imprecision
35	Urate	0.05			0.03	0.38	8%	Tighter	Desirable	Imprecision
36	Urea	1	10	10%	0.5	4	12%	Looser	Desirable	Imprecision
37	Cortisol	30	200	15%	30	150	15%	Same	Optimal	Imprecision
38	Free T4	3	20	15%	1.5	12	12%	Tighter	Desirable	Total Error
39	Free T3	3			0.7	3.5	20%	Tighter	Desirable	Total Error
40	Thyroxine	20	100	20%	12	120	10%	Tighter	Desirable	Total Error
41	Total T3	0.3	2	15%	0.2	1.3	15%	Same	Desirable	Total Error
42	TSH	0.6	4	15%	0.1	0.5	20%	Looser	Desirable	Imprecision

Pilot Study of New ALP's

Two complete sets of General Chemistry Cycle 83 reports using the old and new ALP's were sent to 17 laboratories representing large and small, hospital and community laboratories using a range of instrumentation including those that have 'matrix' issues with the QAP materials. The reviewers were asked to tally the number of outliers they had using the old and new ALP's, including their performance relative to their particular method group, and to give an opinion on the new ALP's. We are grateful to the reviewers for the considerable effort in assessing 14 sets of old and new Interim Reports and 17 assessments of old and new End-of-Cycle reports.

Interim Report Reviews

The number of Interim Report outliers experienced by the 14 Interim Report reviewers was 691 for the old ALP's and 896 for the new ALP's. This represents a mild increase from 1.6 outliers per analyte (10%) with the old ALP's to 2.0 outliers per analyte.

The analytes with the largest proportional increase in outliers were TIBC, Cholesterol, Total Protein, Iron, Albumin, HDLC and Magnesium. All these were expected with tightening of these ALP's except for Cholesterol and HDLC which were loosened at high levels but tightened at the usual levels in the program material.

A few analytes had significantly fewer outliers including Total Bilirubin whose ALP was loosened, but also Calcium and Osmolality where proportional limits were introduced above 2.5 mmol/L and 266 mOsm/kg respectively.

As participants are aware, many outliers in Interim Reports actually fall within method related limits in the Youden plots. It was uncommon for laboratories to have outliers to their method group (0.38 outliers per analyte) and this increased slightly with the new ALP's (0.51 outliers / analyte)

End of Cycle Report Reviews

17 laboratories tabulated the number of analytes that exceeded an ALP of 1.0 on the performance summary graph and also counted the number of analytes that they received an error analysis report for.

The average number of analytes submitted was 30 +/- 4, and the average number exceeding an ALP of 1.0 increased from 12.1 (40%) with the old ALP's to 15.4 (51%) with the new limits. The average number of analytes that received an Error Analysis Report went from 9.6 (32%) to 12.9 (43%). A rise in both of these was expected given that more analytes were 'tightened' than 'loosened'.

The following analyte ALP's have not changed significantly but remain the most troublesome in End-of-Cycle reports: Calcium, Total Bilirubin, Chloride, Sodium, Bicarbonate and Troponin I.

The following analyte ALP's were loosened and are less troublesome in the End-of-Cycle: Osmolality, Urea, TSH, Potassium.

The following analyte ALP's were tightened and were highlighted significantly more often in the new ALP End-of-Cycle reports: Total Protein, HDLC, LD, ALP, Glucose, Albumin and Creatinine.

Summary

As more than twice as many ALP's were tightened (21), as were loosened (8), we may have expected twice as many analytes to exceed their limits as before, however the observed increase was only about 30%. This is because those ALP's that were tightened were only done so when the majority of laboratories (>80%) could achieve that performance.

Parameter	Old ALP's	New ALP's	% Change
Interim: Outliers /analyte	1.6	2.0	25%
Interim: Method Outliers / Analyte	0.38	0.51	37%
EOC: ALP > 1.0	12.1 (40%)	15.4 (51%)	27%
EOC: Error Analysis	9.6 (32%)	12.9 (43%)	34%

In response to the survey of what the reviewers thought the new ALP's, the majority (54%) said they were a slight or large improvement on the old ALP's while 18% thought they were much the same and 27% thought they were slightly worse.

CONCLUSION

It has been the goal of EQA programs around the world to define analytical performance goals that are more clinically relevant than the current goals which tend to be either peer based or expert opinion based. Many EQA's are just starting on the long journey of understanding and applying biological variability based goals while with this announcement, the RCPA Chemical Pathology QAP has finally reached a mature position, a little over ten years since the Stockholm meeting.

Although there will be a slight increase in the number of outliers in the programs from now on, we hope that participants appreciate that the new ALP's are now based on our ability to support clinical decision making. These limits should provide additional confidence in the mathematical principles behind making a diagnosis using any test, but for many analytes it is also a confidence in monitoring patients so that the change in the result is more likely to be due to a change in the patient rather than the impact of analytical uncertainty.

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