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6.1.1.6 Quality Specifications for Detection Limit

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For exogenous quantities which can either cause harm to an individual or whose appearance gives clues to the presence of early disease, the ideal detection limit (IDL) is the smallest amount possible; in practice, this might be tempered by a variety of considerations. For quantities where it is wished to detect simply a change from below to above a stated value (c), or vice versa, IDL can be determined objectively from knowledge of the probability with which this decision is made (z), the random analytical error (s_A), within-subject biological variation s_{Bw}, and changes in systematic error (ΔSE), according to:

$$IDL = c - [\sqrt{2} \cdot z \cdot (s_A^2 + s_{Bw}^2)^{1/2} + \Delta SE].$$

Every analytical method can be fully described in terms of its performance characteristics (1). Much work has been done on delineation of desirable standards for systematic and random components of error, but the ideal would be the availability of quality specifications for all characteristics.

The detection limit (DL) is an important characteristic defined by the International Federation of Clinical Chemistry (1) as the "smallest single result which, with a stated probability, can be distinguished from a suitable blank". Often, the methodological DL is significantly lower than the amount required to be quantitatively measured for clinical purposes (2). However, in other situations, it may be important to carefully define IDL quantitatively and, therefore, objective specifications are required for at least three classes of quantity.

1. Quantities Usually Absent. For quantities which are usually absent (for example, toxic

substances, drugs of misuse, tumour products) and which (a) can cause harm to the individual or (b) can be used as early indicators of disordered structure and function, the ideal specification is to detect the smallest amount of substance concentration possible. This may be tempered by clinical, legal, ethical, economical, or philosophical considerations which may cause methodological DL to be defined in specific quantitative terms.

2. Endogenous Quantities may be present usually in very low concentrations (for example, tumour markers) and it may be clinically important to detect a significant rise above the DL or other threshold concentration defined by clinical considerations.

3. Endogenous Quantities exist (for example, thyrotropin, TSH) for which it is important to detect a fall below the DL or other threshold concentration defined by clinical considerations.

For classes 2 and 3, a model based upon monitoring serial results (3) might be appropriate.

Let the detection limit = DL, and the critical value for clinical decision making, such as the lower reference limit, = c. To detect a fall from the usual concentration to an undetectable concentration, the critical difference (D) depends on (i) the probability that it is wished to use in the decision making which can be expressed in terms of the z-score (z) which is the number of standard deviates appropriate to the probability, (ii) pre-analytical sources of variation such as changes in posture and degree of tourniquet application (s_P), (iii) analytical random error (s_A), (iv) within-subject inherent biological variation (s_{Bw}), and (v) any change in systematic error (ΔSE), according to the formula:

$$D = \sqrt{2} \cdot z \cdot (s_P^2 + s_A^2 + s_{Bw}^2)^{1/2} + \Delta SE$$

When standard sample collection techniques are used, as may be approached in wards and clinics which use skilled phlebotomy services, then s_P approaches zero, and the above formula reduces to:

$$D = \sqrt{2} \cdot z : (s_A^2 + s_{Bw}^2)^{1/2} + \Delta SE$$

But, in this clinical situation, D = c - DL, and thus

$$c - DL = \sqrt{2} \cdot z \cdot (s_A^2 + s_{Bw}^2)^{1/2} + \Delta SE, \text{ or}$$

$$IDL = c - [\sqrt{2} \cdot Z \cdot (s_A^2 + s_{Bw}^2)^{1/2} + \Delta SE]$$

This general formula requires considerable knowledge regarding clinical decision- making for its solution. Therefore, a simpler, more general model might be appropriate.

If the analytical random error meets the generally applicable specification that $s_A < 0.5$ s_B, then $(s_A^2 + s_{Bw}^2)^{1/2}$ will be 1.12 s_{Bw} at most. If it is difficult to determine the probability with which clinical decisions are taken, then $P \leq 0.05$ may be taken as generally useful and so z becomes 1.65 (one-tailed). ΔSE may be considered negligible if the same stable method is used in monitoring. Thus, the simple equation, $IDL = c - 2.6\ s_{Bw}$, gives one approach to calculation of a general quality specification for IDL for a test used simply to monitor either when a subject changes from above to below the decision-making level of quantity, or vice versa.

This model is simple to apply since *c* is usually easy to define and there are many data on s_{Bw} (4-6). As one example, using data from Klee and Hay (7), their "assay B" for TSH has $c = 0.40$ mU/L and $s_A = 0.021$ mU/L at 0.40 mU/L. CV_{Bw} has been estimated as 16.2% (8), 20.2% (9) and 19.3% (10), an average of 18.6% (calculated as mean of variances); therefore, $s_{Bw} = 0.077$ mU/L. Let it be assumed that ΔSE is negligible.

Using the simple model above, the performance required will be:

$$IDL = 0.40 - \sqrt{2} \cdot 1.65 \cdot 1.12 \cdot (0.077) = 0.20 \text{ mU/L},$$

and this might be a suitable quality specification for IDL and for TSH when it is wished to simply detect either when a hypothyroid patient on therapy is being "overtreated" or when a hyperthyroid patient treated with radio-iodine requires replacement.

Since TSH should not fall below the lower reference limit in treated hypothyroid patients, the clinician must react to changes even when the probability is rather low (say 0.80). In this situation z becomes 0.84 (one-tailed) and the specifications for IDL less demanding. Thus:

$$IDL = 0.40 - \sqrt{2} \cdot 0.84 \cdot (0.021^2 + 0.077^2)^{1/2} = 0.30 \text{ mU/L}$$

It should be noted that, in this more general model, the desirable detection limit depends on the value defined for clinical decision-making (c), the probability with which it is required to make the decision (z), the analytical random error (s_A), the change in systematic error (ΔSE) and the inherent within-subject biological variation (s_{Bw}). The IDL required will get lower as analytical imprecision increases and as the certainty with which it is desired to detect a change increases.

Interestingly, it has been proposed (7) that, for TSH, the assay should have less than 1% overlap between the variation of the lower normal value limit and the assay detection limit, ie, the 2.5 percentile of the values in normal adults minus 2.6 times the standard deviation of measurements at this level should exceed the value corresponding to the 2.6 standard deviation limit of the zero pool (separation of lower normal limit from detection limit).

Thus, analytically, $c - 2.6\ s_A > 0 + 2.6\ s_A$, and so $s_A < c/5.2$. This gives the quality specification for the analytical random error required at or near the detection limit and, by inference, the quality specification for IDL; since c = 0.40 mU/L, s_A < 0.08 mU/L and IDL = 0.20 mU/L.

Thus, as has been previously shown in detail for haemoglobin A_{1C} analyses (14), the quality specifications generated from consideration of the clinical situation depends very much on the assumptions made.

Models for IDL based upon other clinical criteria (7) require to be studied. Indeed, it is highly likely that specifications for IDL cannot be based purely on considerations of monitoring individual patients. Moreover, specifications for IDL are probably much related to analytical performance: new methods with lower DL should be encouraged since their application might disclose novel clinical possibilities.

REFERENCES

1. Büttner, J., Borth, R., Boutwell, J.H., Broughton, P.M.G. & Bowyer, R.C. Approved recommendations on quality control in clinical chemistry. Part 1. General principles and terminology. Clin Chim Acta 1979; 98: 129F-143F.

2. Barnett, R.N. Medical significance of laboratory results. Am J Clin Pathol 1968; 50: 671-676.
3. Fraser, C.G., Hyltoft Petersen, P. & Larsen, M.L. Setting analytical goals for random analytical error in specific monitoring situations. Clin Chem 1990; 36: 1625-1628.
4. Ross, J.W. Evalution of precision. In, Werner M, ed. CRC Handbook of Clinical Chemistry. Boca Raton, Fla, CRC Press, 1982, vol 1, pp 391-422.
5. Fraser, C.G. The application of theoretical goals based on biological variation data in clinical chemistry. Arch Pathol Lab Med 1988; 112: 404-415.
6. Fraser, C.G. Biological variation in clinical chemistry. An update: collated data, 1988-1991. Arch Pathol Lab Med 1992; 116: 916-923.
7. Klee, G.G & Hay, I.D. Assessment of sensitive thyrotropin assays for an expanded role in thyroid function testing: proposed criteria for analytic performance and clinical utility. J Clin Endoc Metab 1987; 64:461-71.
8. Browning, M.C.K., Ford, R.P., Callaghan, S.J. & Fraser, C.G. Intra- and interindividual biological variation of five analytes used in assessing thyroid function: implications for necessary standards of performance and the interpretation of results. Clin Chem 1986; 22: 962-6.
9. Browning, M.C.K., Bennet, W.M., Kirkaldy, A.J. & Jung, R.T. Intra-individual variation of thyroxine, triiodothyronine, and thyrotropin in treated hypothyroid patients: implications for monitoring replacement therapy. Clin Chem 1988;34:696-699.
10. Ricos, C. & Arbos, M.A. Quality goals for hormone testing. Ann Clin Biochem 1990; 27:353-358.
11. Larsen, M.L., Fraser, C.G. & Hyltoft Petersen, P. A comparison of analytical goals for haemoglobin A1C assays derived using different strategies. Ann Clin Biochem 1991;28:272-278.

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