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The Thistle QA CEU No is: **MT00025**.

Each attendee should claim **THREE** CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

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Is variation in biological variation a problem?

The Concept of Biological Variation (BV) has been known for many years, with several excellent reviews and books published on the subject. BV is a component of the total variation (CV_T) and can be considered in terms of intra-individual (BV_I) and inter-individual (BV_G) variation. For a given individual the BV_I can be determined from the total variation (CV_T) and the analytical variation (CV_A). Since the CV_A can be readily calculated for most analytes the BV_I can be readily determined. BV_I should reflect 'random' variation; it should be independent of method and analytical variance. Non-random variations such as effects of diet, menstrual cycle, seasonal variation, age, sex, etc, must be taken into account before the BV is determined. Pre-analytical variables, such as collection tube type, sampling technique, etc, also need to be minimized to enable an accurate BV_I to be determined.

A database of mean BVs can be used to help in the determination of reference range and the calculation of what are significant changes in an analyte, termed the Reference Change Value (RCV), a vital component when monitoring patients.

The RCV for any analyte is usually determined on healthy individuals. Carmen Ricós and colleagues (Ricós C, Iglesias N, García-Lario JV, *et al*. Within-subject biological variation in disease: collated data and clinical consequences. *Ann Clin Biochem* 2007; **44**: 357-66) ask if the RCV was the same in disease as it is in health. If the RCV does change in disease, this will have a fundamental bearing on how we determine what are clinically significant changes when monitoring patients.

From their literature review, we can be reassured that the majority of BVs remain the same in disease as in health. Using PSA as an example, the BV has been shown to be the same in healthy men and those with stable prostate cancer. Employing the BV_I in healthy men along with average CV_A for the majority of PSA assays commercially available, a change of PSA of 50% or greater can be considered clinically significant. This figure is commonly used by laboratories clinicians.

However, Ricós *et al.* do provide evidence that nine analytes have different BV in health and disease. These are:

- * Alpha-fetoprotein in hepatic disease;
- * Alkaline Phosphatase in Paget's disease;
- * CA 125 in ovarian cancer
- * CA 15.3 in ovarian cancer;
- * Carcinoembryonic antigen in colorectal cancer;
- * Creatinine in kidney disease;
- * HbA1C in diabetes mellitus;
- * Lipoprotein (a) in diabetes mellitus;
- * Urine albumin creatinine ratio.

For each analyte the BV_I was higher in the disease state than in health, and furthermore, it was the index disease which was the BV variant; for example HbA1C in diabetes. The authors state that if the BV does differ in health and disease, we need to employ different RCV than those normally used. Before we move forwards with such a plan perhaps we need to reflect upon what BV is and why should it vary in health and disease?

BV is random variation, and for each analyte it would be made up of different factors. For example, with PSA the random variation could be due to variations in cell turnover, PSA synthesis and clearance from the blood. Clearly these factors could be altered in the disease state, but would they become more variable for an individual? Theoretically it may be possible that the increased size of a prostate gland and/or the greater number of cells producing PSA could make them more susceptible to large changes due to possible 'random' events which may stimulate the release of PSA into the bloodstream. In practice this does not appear to be a problem. However, considering the clinical consequences of adopting disease-specific RCVs, we need to be certain that they are credible.

Many factors will influence the calculation of CV_I and this may be reflected in the wide ranges of CV_I that have been determined for any analyte. The number of measurements, frequency, time span over which the measurements have been made plus the total number of individuals assessed could all influence the determination of average CV_I being determined. Once again taking PSA as an example, the BV_I varies from 2.1 to 22.9%. It has been suggested that these variations in BV are important when assessing serum lipids and hsCRP. Other factors may effect CV_I – for example, the degree of cross-reactivity in immunoassays, or non-creatinine interferences in the Jaffé reaction, especially at the bottom end of the measured values. Is it possible to compare average BV from several studies to a BV determined in disease?

Finally, as with all these types of studies there will always be the problem of deciding when and for how long a disease is stable.

Due to all these uncertainties, before we adopt disease-specific RCVs the CV_I in health and disease, carefully controlled experiments employing identical pre-analytical, analytical and well matched patients and controls will be required. It is hoped that Ricós and colleagues continue to refine their exceedingly useful database, and we may find we can lower the variation in BV in both health and disease.

CPD Questions:

1. What makes RCV such an important component of patient care?
2. List three factors affecting the BV for PSA.