

Bob Barrett:

This is the podcast from '*Clinical Chemistry*'. I am Bob Barrett. Many measurements made by medical laboratories are made not for a primary diagnosis, but rather monitoring health or disease status of an individual.

One of the suggested ways of aiding interpretation of differences that may be seen over time is the use of Reference Change Values or RCVs. These are the values that are due to inherent sources of variation, mainly analytical and within-subject biological variation and that must be exceeded for a significant difference to have occurred.

The concept has been around for many years and there are many publications on analytical and biological variation, but RCVs do not seem to have been well accepted. Here, to talk about why that may be the case is Professor Callum Fraser from Dundee in Scotland.

Dr. Fraser has published and presented much on biological variation and the setting of analytical goals and is the author of the book '*Biological Variation: From Principles to Practice*,' published by AACC press. For the December 2011 issue of '*Clinical Chemistry*,' he prepared an editorial on the topic.

Dr. Fraser, while you and others have published extensively on biological variation, the within subject biological variation is not known for all the analytes examined in laboratory medicine, it seems that it would be difficult to evaluate this for analytes not normally present, such as monoclonal proteins or in children or samples such as arterial blood gases. How would you tackle these issues?

Dr. Callum Fraser:

Yes, this is a very interesting question and I do agree that for some analytes it is always very, very challenging to define, the within-subject biological variation. However, I really do believe these difficulties could be overcome by very careful and judicious selection of a reference population of subjects to examine.

In my recent editorial in '*Clinical Chemistry*,' I've pointed to some examples of Jewish studies done on monoclonal proteins in stable patients with disease. I've also pointed to a wonderful study done on glycosylated hemoglobin in children with cystic fibrosis and there's another work, a recent work on electrolytes in people -- patients actually in intensive care.

So these sorts of populations can be studied to find biological variation estimates, but it is difficult, and the identification of appropriate reference populations does require a better flair and imagination. Firstly, I would really encourage further insightful efforts and further studies

looking at these difficult quantities with interesting and noble reference populations.

Bob Barrett: There are databases of estimates within-subject biological variation, but some think that these are not of the highest quality and can't be used in day-to-day practice. On the other hand you are a very strong advocate for the use of RCV, why is that?

Dr. Callum Fraser: For some analytes the estimates are very, very robust, the estimates of within-subject biological variation in particular. Commonly examined analytes have been the subject of many, many studies over the years on biological variation and these estimates are very robust.

Moreover, my personal view is that the estimates are within-subject biological variation, the quantitative estimates; I actually represent a quantitation of the magnitude of homeostatic mechanisms in a single species, the homo sapiens, and therefore, they should be constant over time in geography and population.

And there's very good evidence that this hypothesis actually generally holds, and it holds even in chronic but stable disease where the estimates are actually very similar to those in healthy individuals.

Bob Barrett: Isn't there a particular problem with some analytes, for example, those that are measured by immunoassay, where the estimates of biological variation do seem to differ somewhat?

Dr. Callum Fraser: That is true, and estimates do differ for some quantities, and I think the lack of agreement in the public studies of biological variation in such quantities might well be due to a lack of real rigor in the design and execution of some of the experiments done.

However, I think the problem here with immunoassays is not that the studies are in any recess state. I think the real problem is because what is being analyzed, the quantity that is being examined is actually not very well defined in these studies and in consequence dissimilar quantities are actually being regarded by readers and others as a single quantity.

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For example, currently there is a great interest in the biological variation of the Cardiac Troponins. In Cardiac Troponin I, there are several methods available for Cardiac Troponin I, which actually measure different things, because the anti-bodies react with different parts of the molecules.

So they refer to all as Cardiac Troponin I, but we are actually measuring different quantities, and I think the problem can be solved, the problem that we seem to have different estimates of biological variation for the same quantity, because we really have different quantities and if we as clinical chemists actually, we're very careful in defining the name of the manufacturer, as well as the method, and in fact, the date of this study, because some methods change with time, then it would be quite clear which estimates to combine into a single estimate, and which should be retained separately as a different quantity with a different name.

Bob Barrett: Well, regarding the calculation of RCV, what analytical imprecision values would you use in the calculation, since for some methods these vary significantly over the reportable range of the assay?

Dr. Callum Fraser: And indeed it does, and I think one must think about current methodology and technology. When the analytical imprecision becomes small, as it does with new techniques, as compared to within-subject biological variation, then it really doesn't matter very much, because the analytical imprecision actually contributes very, very little to their Reference Change Value.

And of course, for these RCV Reference Change Value calculations, the biological variation component can be obtained from the literature, from the databases on biological variation, but the analytical imprecision component should be generated by each laboratory using its own internal quality control schemes, and when calculating the Reference Change Value the analytical imprecision that's appropriate at clinical decision-making levels should be the one, irrespective of the analytical imprecision magnitude, which is used to calculate the RCV for use in the laboratory.

Bob Barrett: Well finally doctor, how can the use of RCV be improved?

Dr. Callum Fraser: Well, firstly I'm convinced that tools such as the RCV that help interpretation of the difference between the serial results in an individual is very important information that should be included actually on clinical laboratory reports, as some of us have done for many years, and I believe that the Reference Change Value concept provides simple and effective aids for all laboratories. They certainly have either more objective than many of the round number recommendations as beloved by our guideline makers.

However, along with their problems, and I advocate that as detailed in my editorial, they do need to be better used and there are two aspects to this. One, is that the probability

that the clinical decision is being made should be taken into account, because in medicine, we don't always make decisions at 95% probability. In research we use 95% probability, but in practice we do not.

And the second aspect of course, is that change, rise, fall, increase, decrease, these ones actually mean different things, and as we're talking about arise or a fall or an increase or a decrease, then this is a one-sided or one-tailed decision, whereas change can mean either increase or decrease, and is what is called a two-tailed or two-sided decision.

And for these situations, different Z scores must be used in RCV formula to get the critical difference or the Reference Change Value that is appropriate to the actual clinical decision being made. So I do think that there are improvements that can be made at the moment with current knowledge, however, as with everything else in laboratory medicine, the concept is advantageous, but it is not without disadvantages, and I would hope that my colleagues, and my friends, and younger people in laboratory medicine will take the opportunity to think about newer ways to look at differences in serial laboratory results, and I look forward to reading their publications in the future.

Bob Barrett: Professor Callum Fraser's editorial on biological variation appears in the December 2011 issue of '*Clinical Chemistry*.' Dr. Fraser's been our guest in this podcast. From '*Clinical Chemistry*,' I'm Bob Barrett. Thanks for listening.

Total Duration 10 Minutes