Primer on Understanding Lab Values

It is no surprise to find that laboratory data and interpretation is very important to clinicians. Nearly 80% of physicians' medical decisions are based on information provided by laboratory reports.1 And, of course, a test result by itself is of little value unless it is reported with enough appropriate information for that clinician to make an intelligent interpretation. Typically, this information is provided in the form of a reference range (RR), reference interval (RI), or medical decision limit. At Sanesco, the Correlation Analysis report adds even more valuable information and support to the standard lab values. A RR or RI as defined by Ceriotti "is an interval that, when applied to the population serviced by the laboratory correctly includes most of the subjects with characteristics similar to the reference group and excludes the others."2 Remember, no RR is either completely "right" or "wrong." The majority of RRs in use today refer to the central 95% (that is, 2 standard deviations from the mean) of the reference population of subjects. Thus, by definition, 5% of all results from "healthy" people will fall outside of the reported RR and, as such, will be flagged as being "abnormal." Labs can set these "confidence limits" wherever they feel it is most appropriate for their population – at 5%, 10% or even 20%.

There can be lots of problems associated with the calculation of RR. The Clinical and Laboratory Standards Institute approved guideline, "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory," recognizes the inherent difficulties and controversies surrounding the establishment of RRs and the verification process: "…the working group recognizes the reality that, in practice, very few laboratories perform their own reference interval studies," "…instead of performing a new reference interval study, laboratories and manufacturers refer to studies done many decades ago, when both the methods and the population were very different."3

It should also be noted that in the guideline "Health is a relative condition lacking a universal definition. Defining what is considered healthy becomes the initial problem in any study…."3 In reality, there will always be some level of uncertainty with a given selection protocol not only because of the definition of health that was selected but also because of the very real possibility that some of the selected subjects may, in fact, have subclinical disease.4 When gathering the population upon which the RR study will be done, we do our best to "weed out" patients who would be considered "abnormal" by means of their medical history or medication history. But this process is certainly not without problems which can cause the RR data to become skewed – particularly if the study population number is not very large.

Recruiting the appropriate group of reference subjects and obtaining informed consent in today's environment is costly, time-intensive, and virtually an impossible task for most laboratories. Not everyone is willing to budget the appropriate resources for a lengthy and expensive RR study. The challenges are further magnified in establishing RRs for different age groups (eg, pediatric patients for example), timed collections, or serial measurements. Many laboratories elect to "transfer" the RRs that were in use with an older method (or from another laboratory) to a new method. To accomplish this, the first step is for the laboratory to demonstrate the 2 methods produce comparable results. We know that analytic systems drift over time, and there is certainly no guarantee that the method used today is producing results anywhere near the results that were produced at the time of the original RR study. Having said that, this technique is the main reason why many laboratories today are using RRs that were established decades ago and are therefore out-of-date.4

With all these limitations, it might surprise you that Sanesco regularly updates our reference ranges as was done recently this past year. It is a major time commitment and expenditure, and we feel it is the right thing to do for you, the customer. It is all part of NeuroLab's Quality Assurance Program which includes regular blinded test

submissions to Bio-Rad (a world leader in Lab QA), and all of our laboratory certifications - including our most recent successful inspection with COLA.

As a matter of fact, as many of you know, our most recent RR study caused a number of changes in the way we report our lab values to you. What we found was a significant drift from earlier RRs. What we ended up with was a near-classic Gaussian distribution (Bell-shaped curve) with a very large peak in the middle of the distribution. What this did when we placed the 95% limits on the distribution was to encompass nearly the entire population of our patients within those constraints - leaving us with fewer people outside the range and less valuable numbers (in terms of treatment options) for the clinician. As a lab with integrity, we had to remain true to the numbers we discovered with the RR study. Otherwise, what is the use of having a lab?

That is when we added the "Optimal Range". We knew that although the "normal population" may have drifted from prior RR studies, that most people (based on our data from both patient questionnaires and lab values) felt better and performed better with higher levels of serotonin or GABA, for instance.

Perhaps we can draw some analogies from what happened with the study of cholesterol in the late 80's until the early twenty-first century. Measuring cholesterol levels is an example of a laboratory test which is used to define as well as to prevent a disease – that is, hypercholesterolemia. Early studies in the US placed the upper normal reference range limit for serum total cholesterol in the 300-320 mg/dL range. But in Japanese populations, the same statistical procedures gave lower limits of 240-250 mg/d. This led Framingham data being reevaluated and the suggestion of lowering the limit to 220 mg/dL.5 One Clinical Chemistry reference at the time stated "Although the ranges shown have been established for apparently normal, healthy adults, these may not necessarily be "desirable" values".6 Desirable or "Optimal" ranges for cholesterol continue to be a subject of controversy. While some may argue that dropping the levels to their current state (LDL of 70 for those with diabetes or a history of heart disease, for instance) is an attempt for drug companies to increase their profits, the landscape continues to change.

This is one reason we have never tried to define any disease with Sanesco's testing. We continue to think of it not as a diagnostic tool, but as a clinical tool designed to help doctors and patients make better decisions as they work together. As a result of the new "Normal" reference ranges and the institution of our "Optimal Ranges", you have a new report format. We have updated the report slightly to delineate "high" and "low" values to support our belief that keeping our patients in the "Optimal Range" will offer more benefit to both patient and provider by more accurately reflecting their clinical state. We sincerely hope this will provide you, the clinician, with an easy-to-understand clinical tool to help you monitor and correct your patients' neurotransmitter and hormonal imbalances.

References

1. Utah Governor Huntsman recognizes medical laboratory week. Clinical Lab Products. Issue Stories. May 2006. http://www.clpmag.com/issues/articles/2006-05_03.asp. Accessed April 9,2014.
2. Ceriotti F. Prerequisites for use of common reference intervals. Clin Biochem Rev. 2007;28:115-121.
3. Clinical and Laboratory Standards Institute. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline. Third Edition. CLSI document C28-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.
4. Katayev,A, et al. Establishing Reference Intervals for Clinical Laboratory Test Results - Is There a Better Way?. Am J Clin Pathol 2010;133:180-186.

5. Usui T, [A concept for normal range of serum cholesterol]. Rinsho Byori 1991; 39(5): 483-8.
6. Tietz NW, Fundamentals of clinical chemistry, 3rd ed. W.B. Saunders, Philadelphia, 1987.