Biochemistry & Analytical Biochemistry

Yadav, Biochem Anal Biochem 2015, 4:4
DOI: 10.4172/2161-1009.1000e158

Editorial Open Access

Reference Interval for Clinical Laboratory Test Parameters

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Editorial

Health care delivery is no longer a simple process of examining the patient and giving him a prescription. Over the years there has been rapid expansion in the various and giving of health care services. As part of this expansion process and explosion of scientific medical knowledge, it is hard to underestimate the importance of clinical laboratory test results. Nearly 80% of physicians' medical decisions are based on information provided by laboratory reports. A test result by itself is of little value unless it is reported with the appropriate information for its interpretation. Typically, this information is provided in the form of a reference interval (RI) or medical decision limit. The concept of reference interval was introduced by International Federation of Clinical Chemistry (IFCC) to avoid the problems with normal values and values obtained from an individual under clinical investigations. According to IFCC, it is necessary for every laboratory to have its own set of reference limits [1].

An 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". No RI is completely right or wrong [2]. The majority of RIs in use today refer to the central 95% of the reference population of subjects. By definition, 5% of all results from healthy people will fall outside of the reported RI and, as such, will be flagged as being abnormal. They may also be used in clinical trials as a guide to setting inclusion / exclusion criteria as well as the basis of safety monitoring for trial participants.

An important part of medical decision in diagnosis is dependent on comparison of patient related observations with reference values; hence it is critical enough to establish the reference intervals for a particular population. The reliability of an RI study should be a function of its accuracy and reproducibility and have a direct relationship with the number of observations used and method standardization. Reference ranges are established by testing the large number of healthy population and figuring out what appears to be "Normal" for them. However, it is critical to define the reference population. Demographically, it should match the population whose laboratory results will be compared to this reference range. For developing a normal reference interval for a laboratory, a minimum of 120 samples should be collected from the normal individuals for analysis, by a non parametric means for each partition (e.g, gender, different age group)4 and this should be done after a specific time period because reference ranges may change with time and also the methods. If this seems to be a difficult option for a laboratory, they can use alternative by verifying the reference ranges developed by other laboratory in the same population.

The reference range will vary, depending on the age, sex and race of a population, and even the instruments the laboratory uses to perform the tests. Furthermore, by definition, 5% of the normal population will fall outside the reference range. Factors other than medical conditions can affect laboratory values, such as male or female sex, diet, use of drugs (prescribed, over-the-counter and herbal remedies), and stress, as well as other more exotic factors like altitude.

Most medical laboratories provide reference data for all examinations that may be ordered, commonly in the form of reference intervals for healthy individuals. A 95% reference interval usually is bounded by two limiting values and contains 95% of the values found in healthy individuals. Since laboratory results often are dependent on sex and age, it is often necessary to have separate reference intervals for the two sexes and/or for different age groups. A laboratory result located outside the corresponding health-related reference interval does not necessarily imply that the individual is diseased or at risk.

In the past, many hospital laboratories have either used the reference interval recommended by the instrument of test manufacturer or the values published in medical or laboratory textbooks. Because of the diversity of instrumentation, methodologies, reagents, and populations, it is important that moderate – to large-sized hospital laboratories determine their own reference interval.

As is the case for all scientific data, the clinical laboratory test result has no value in isolation. There needs to be some control, standard or reference value for comparison. Comparison is as fundamental to clinical medicine as it is to any other scientific discipline. When doctors note clinical signs and symptoms during clinical examination and interview, they consciously or subconsciously make reference to a database of signs and symptoms associated with disease for comparison with those presenting in their patient. Similarly, interpretation of a laboratory test result is a process of comparison. The type of reference used for comparison depends on the nature of the clinical question being asked of the laboratory test. For example, if the test is being used to monitor a specific disease process, previous test results from that patient might be the most appropriate reference for comparison; serial concentration of blood tumor markers to assess response to cancer therapy is a nice exemplar. Some laboratory tests are used not for diagnosis or monitoring but to make specific clinical decisions. For example, measurement of serum cholesterol is most often used for assessment of cardiovascular disease risk and to determine if cholesterol-lowering advice/drugs are indicated. In such circumstances a particular concentration of the analyte, known as the "decision limit", has to be defined. The decision limit is then the reference for comparison. Some laboratory tests are used to monitor drug therapy. Here patient results are compared with a so-called "therapeutic range, which defines the range of drug concentration in blood consistent with maximum therapeutic and minimum adverse (toxic) effect.

Despite progress in the conceptual aspects of reference values, in practice their use is still not entirely satisfactory. There are two major

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Received: September 09, 2015; **Accepted:** September 10, 2015; **Published** September 12, 2015

Citation: Yadav D (2015) Reference Interval for Clinical Laboratory Test Parameters. Biochem Anal Biochem 4: e158. doi:10.4172/2161-1009.1000e158

reasons for this unsatisfactory situation. One factor is the meteorological uncertainty of measurements, particularly with regard to their trueness and method dependence. This uncertainty jeopardizes the transferability of reference values over time and between laboratories, despite proposed biological variation-derived analytical accuracy goals aimed at achieving acceptable transferability of both Gaussian and non-Gaussian distributed reference values. The second difficulty involves comprehensively defining a reference population appropriately matching the specific patient(s) referred to the laboratory and extracting from such a population a numerically consistent sample group of individuals to be enrolled as "reference individuals". The establishment of a suitable reference population is essential but difficult, and there are still cases in which unrepresentative reference populations medical students, hospital employees, blood donors or other volunteers, variably classified as "healthy" – have been used. Attempts have been made to overcome these difficulties by using hospital or primary healthcare patients and applying different criteria in the detection of outlying data values and the identification of non-diseased individuals.

The reference values concept has been adopted by health care professionals, including clinical chemists, laboratory scientists, and clinicians and simultaneously by all the official organizations in charge of the establishment of legislation. But the estimation of reference limits, and the evaluation of biological variability need to be improved at the level of the procedures, which are currently too long and too expensive and not feasible easily for all laboratories. The procedures for obtaining reference values, if we follow the original documents, are complex, and that is the main reason that clinical chemists or diagnostic kit manufacturers have not used them systematically. There is clearly a need that scientific societies and international organizations propose practical recommendations.

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