October 24-25, 2015
Zagreb, Croatia

EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

15th EFLM Continuous Postgraduate Course in Clinical Chemistry and Laboratory Medicine

VERIFICATION OF REFERENCE INTERVALS

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15th EFLM Continuous Postgraduate Course in Clinical Chemistry and Laboratory Medicine
October 24-25, 2015 – Zagreb, Croatia

THE LABORATORY IN DIAGNOSIS

JAMA 100 YEARS AGO
FEBRUARY 9, 1907

THE LABORATORY IN DIAGNOSIS.

The use of laboratory methods in diagnosis is, for the most part, a growth of recent years. While it is true that the laboratory examination of the urine is a procedure which has been practiced by several generations of physicians, the more complicated hematologic, bacteriologic and serologic examinations have come into general use only recently. It probably no exaggeration to state that fifteen years ag there were not half a dozen medical schools in the Unite States in which a laboratory course in clinical diagnosis wa given. Even ten years ago such courses were rare, and at the present time there are many schools in which they either are entirely inadequate or do not exist. The reasons for this lies in the fact that such courses require expensive appara tus, are time consuming, and need men with special train ing as instructors. In the average medical school instruction in clinical microscopy is seldom given in a hospital, and the subject is often taught by the professor of pathology, who most likely, has excellent laboratory training, but little clinical experience. In comparatively few schools has the student the opportunity of applying the laboratory methods at the bedside, for in the majority of American schools bed side instruction worthy of the name does not exist.

It is perhaps fair to say that the average physician of to-day has to re-establish in the science of medicine and to pro nounce a new office art. The medical profession has been striv ing so long to drag itself out of the realms of the purely empiri cal, and has achieved so much in this direction along certain purely scientific lines, that the practitioner, whose laboratory training is, after all, only rudimentary, is apt to overestimate the value of laboratory procedure, and to forget that the appli cation of laboratory methods to clinical medicine is new, and that the results are not to be compared in accuracy with those of the pure, as distinguished from the applied, sciences.

We would be the last to deny that advances of the most far-reaching character have been made by laboratory work ers in the last one hundred years. Our whole conception of certain classes of diseases has been changed by the work of labo ratories, and the treatment of some bacterial diseases has been taken from an empirical and placed on a rational basis by the pure scientists of the profession. All this we acknowledge and glory in, and we would suggest that the glamor [sic] which surrounds these brilliant laboratory achievements is one fac tor which leads the average practitioner to place too high a value on laboratory diagnosis. No one will acknowledge more quickly than the laboratory workers themselves that labora tory diagnosis only reaches its highest usefulness when the findings of the bench are correlated with the findings of the bedside. The profession must learn that, in most instances, the result of a laboratory test should have, in a given case, the same value as a physical symptom or an approved clinical sign. Too many men order this test, and fail to correlate the laboratory findings with the clinical findings. Too many sit back in their easy chairs, so to speak, waiting for the laboratory to solve a problem whose solution can often be just as accurately reached by the use of their own senses and fingers.

There is danger that occasionally laboratory findings may be allowed to take the place of the keen thinking and the edu cated senses which our professional ancestors had to such good purpose. It lies in the hands of the clinical teachers of this country to overcome the obvious tendencies in this direction. Every practitioner should preferably do his own labo ratory work, and, if this is impossible, he should at least know how to properly interpret and correlate the findings of oth ers. Too many errors are made when the physician, lacking in knowledge of the significance of laboratory findings, relies on the reports of the pathologist who lacks in clinical expe rience, and who bases his returns on the examination of ab stract specimens from a concrete patient of whose history he is usually almost completely ignorant.

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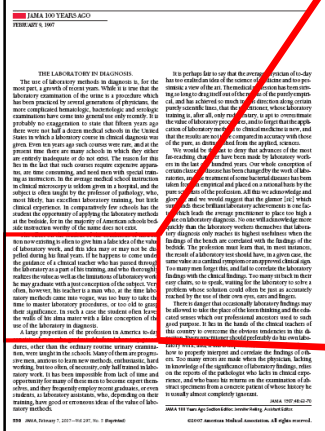

The effect on the student of the conditions of instruction now existing is often to give him a false idea of the value of laboratory work, and this idea may or may not be dispelled during his final years. If he happens to come under the guidance of a clinical teacher who has passed through the laboratory as a part of his training, and who thoroughly realizes the value as well as the limitations of laboratory work, he may graduate with a just conception of the subject. Very often, however, his teacher is a man who, at the time laboratory methods came into vogue, was too busy to take the time to master laboratory procedures, or too old to grasp their significance. In such a case the student often leaves the walls of his alma mater with a false conception of the use of the laboratory in diagnosis.

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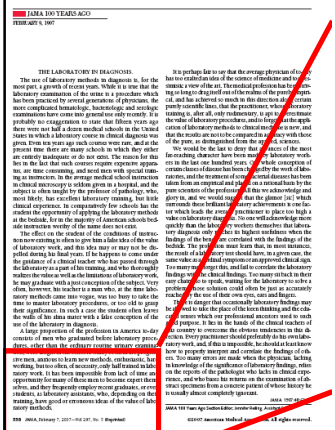
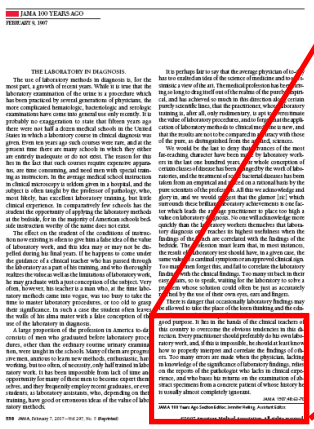


A large proportion of the profession in America to-day consists of men who graduated before laboratory procedures, other than the ordinary routine urinary examination, were taught in the schools. Many of them are progressive men, anxious to learn new methods, enthusiastic, hard working, but too often, of necessity, only half trained in laboratory work. It has been impossible from lack of time and opportunity for many of these men to become expert themselves, and they frequently employ recent graduates, or even students, as laboratory assistants, who, depending on their training, have good or erroneous ideas of the value of laboratory methods.

THE LABORATORY IN DIAGNOSIS



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One hundred years of laboratory testing and patient safety

Giuseppe Lippi[1], Gian Cesare Guidi[1] and Mario Plebani[2,*]

Generally, little attention is paid by most medical journals to the role of laboratory professionals worldwide. We were rather surprised to read the article entitled "The laboratory diagnosis", recently published in the Journal of the American Medical Association (JAMA) (1). Although this manuscript was drafted nearly 100 years ago, it is noteworthy that the situation has not changed very much and the clinical-laboratory interface is still struggling with similar issues.

The aim of a Clinical Laboratory Test is to determine the concentration or activity of a diagnostically relevant analyte in a body fluid in order to provide information on the clinical situation of a patient.

CLIA '88

Perhaps most notable was a Pulitzer-prize winning series that was broadcasted by a Washington, D.C., television station, and followed by a compelling article in the Feb. 2, 1987, edition of *The Wall Street Journal* that highlighted scandals involving several commercial laboratories which inaccurately analyzed Pap smears. Several women died from undetected cervical cancer because of these inaccurately analyzed tests. Of the tens of thousands of laboratories run by physicians at that time, only a handful performed cytology testing, but the public demanded that Congress take action in response to these preventable deaths. Congress reacted by holding oversight hearings which ultimately guided the drafting of CLIA '88, which later was signed into public law (PL 100-578) on Oct. 31, 1988.The law is far-reaching and regulates POL testing on a national scale.

GOVERNOR HUNTSMAN PROCLAIMS MEDICAL LABORATORY WEEK N UTAH

SALT LAKE CITY April 12, 2006—Governor Jon Huntsman, Jr., today signed a proclamation declaring April 23–29, 2006, as Medical Laboratory Week in Utah. For the 31st year in a row, his celebratory week, observed nationally by medical laboratory professionals, will recognize the contributions of the scientific and technical personnel whose work in the clinical laboratory helps give our nation the best possible health care.

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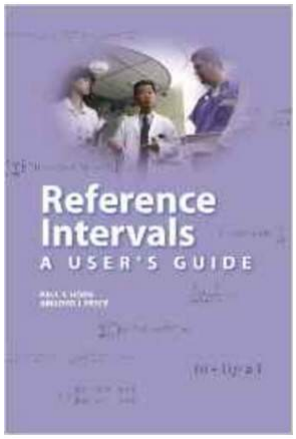
In Schneider's 1960s paper entitled "Some thoughts on normal, or standard, values in clinical medicine", he states: "… practical medicine is basically founded on comparison. If medicine is to be scientific, we must not only understand the structural, functional and chemical relations operating in individuals, but we must also understand the basis of our comparisons…

According to Horn and Pesce: "the reference interval is the most widely used medical decision-making tool", even if its practical usefulness is lower than its theoretical power. This is due to the fact that obtaining a "good" reference interval is a very demanding activity, in terms of time, money and knowledge.



Commentary

Prerequisites for Use of Common Reference Intervals

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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.[1] 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. 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."[2(p115)] No RI is completely "right" or "wrong." 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."

Clinical Chemistry / Estimating Reference Intervals

Establishing Reference Intervals for Clinical Laboratory Test Results

Is There a Better Way?

Alex Katayev, MD,[1] Claudiu Balciza,[2] and David W. Seccombe, MD, PhD[3]

Key Words: Reference; Interval; Estimation; Laboratory; Test; Result; Interpretation

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There are many problems associated with the calculation of RI. The latest edition of the Clinical and Laboratory Standards Institute–approved guideline, "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory," recognizes the difficulties and controversies surrounding the establishment of RIs 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(p1)]

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Recruiting a valid group of reference subjects and obtaining informed consent in today's environment is costly, time-intensive, and virtually an impossible task for most laboratories. The challenge is further magnified in establishing RIs for different age groups (eg, pediatric patients and geriatric patients), uncommon sample types (eg, cerebrospinal fluid and aspirations), timed collections, challenge tests, and serial measurements.


Establishing Reference Intervals for Clinical Laboratory Test Results
Is There a Better Way?

A laboratory can elect to "transfer" the RIs that were in use with an older method (or from another laboratory) to a new method. To do this, the laboratory must first demonstrate that the 2 methods produce comparable results. It is well known that analytic systems drift over time, and there is no guarantee that the method of today is producing results that are comparable to those that were produced at the time of the original RI study. This technique is the main reason why many laboratories today are using RIs that were established decades ago and are out-of-date.

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An alternative approach for establishing RIs is to do an indirect so-called a posteriori study of the patient data already collected and stored in the laboratory database. This is appealing because the data are readily available and will result in time and cost savings. A number of publications discuss this approach.[4-8] Most of these studies were able to report clinically relevant and meaningful RIs. All of them used various sophisticated filters to exclude results from "unhealthy" subjects, and some used data from hospital laboratories and some from outpatient care settings or noninstitutionalized population study databases. Most of these studies used complex statistical algorithms to derive the final intervals. However, current guidelines do not endorse these methods as a primary approach for establishing RIs, mainly out of concern for the fact that most of the data may not come from reference or healthy subjects.[3] This position may be justified for test results collected from hospitalized patients but is questionable when considering a very large number of results that have been collected in outpatient settings.


Establishing Reference Intervals for Clinical Laboratory Test Results
Is There a Better Way?

Prerequisites for Use of Common Reference Intervals

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But what is meant by a "good" reference interval? It 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. Usually we consider "health-related" reference intervals to mean that the subjects with values within the interval have a lower probability of being affected by a specific disease, while those outside the interval have a higher statistical probability of having the disease or, at least, that the observed value is not normal for a healthy person. The percentage of unhealthy people included in the reference interval or, vice versa, the percentage of healthy subjects outside the interval, defines the "goodness" of the interval.

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The factors responsible for this misclassification were already recognised by Schneider who identified the three contributing causes namely, intraindividual, interindividual and analytical variability.[1] Intra- and interindividual variability are inextricably bound. Nevertheless, the relative sizes of these two sources of variation can substantially affect the usefulness of the reference interval as a guide to the status of an individual.

One way to improve the usefulness of reference intervals is to reduce the interindividual variability by partitioning the intervals as much as possible. Stratification by age and gender is the minimum pre-requisite, but other ways include by race, ethnic group, body mass index or nutritional habits (e.g. vegetarians). Herein is the problem of the selection of an appropriate number of reference subjects, properly screened to exclude relevant pathologies, and subdivided by gender, age, race, ethnicity and lifestyle.

Commentary

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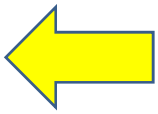
Particularly, the source of reference intervals may be quite different and heterogeneous (manufacturer's recommendation, textbooks and literature, internal studies by healthy volunteers testing, other laboratories, undefined) (11, 12). To try to minimize these differences among laboratories, results are often expressed as multiples of the upper reference limit (URL). This approach has been used in international guidelines (13) and some authors in the past welcomed it as "physician liberation units" (14). Recently, it was proposed a more sophisticated version of that approach called "quantity quotient reporting" (15). Studies have demonstrated, however, that the expression of results as URL multiples paradoxically increases the scatter of results due to both inter-method differences and the different laboratory reference limits (16).



Clin Chem Lab Med 2012;50(5):813–817 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/CCLM.2011.828

Opinion Paper

Obtaining reference intervals traceable to reference measurement systems: is it possible, who is responsible, what is the strategy?

Mauro Panteghini[1,*] and Ferruccio Ceriotti[2]

Cautions needed in the adoption of traceable reference intervals

Boyd has cautioned against the uncritical use of "common" reference intervals, stressing the need to fully document the possible presence of differences in tests results across populations due to biological or environmental factors (22). Until it can be reasonably shown that no differences exist for a given test between the population served by individual laboratories and that used in defining traceable reference intervals, their adoption should indeed be discouraged.

The selection of individuals for the production of reference values needs much attention. Selection of "normal reference" subjects is from many years a key point in all recommendations for the development of reference intervals (23)

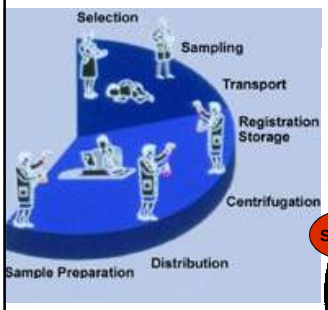
Opinion Paper

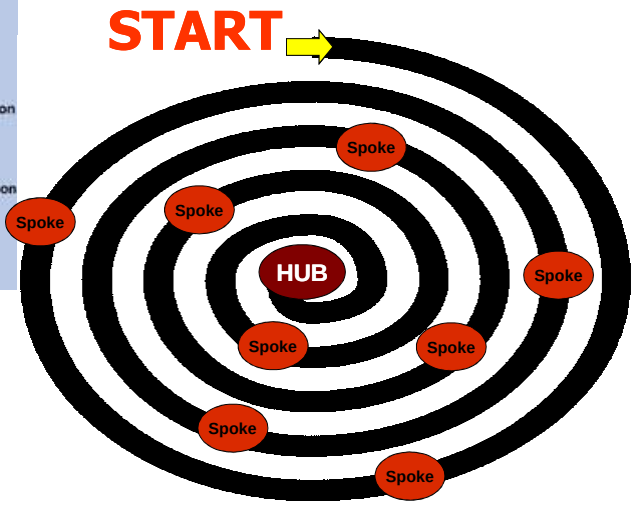
Obtaining reference intervals traceable to reference measurement systems: is it possible, who is responsible, what is the strategy?

INTERNATIONAL JOURNAL OF LABORATORY HEMATOLOGY

Influence of temperature and time before centrifugation of specimens for routine coagulation testing

G. L. SALVAGNO*, G. LIPPI*, M. MONTAGNANA*, M. FRANCHINI†, G. POLI*, G. C. GUIDI*





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Review Article *Ann Clin Biochem* 2009; 46: 8–17. DOI: 10.1258/acb.2008.008170

Reference intervals: the way forward

Ferruccio Ceriotti[1], Rolf Hinzmann[2] and Mauro Panteghini[3]

Table 3 Differences between reference intervals and decision limits

	Reference intervals	Decision limits
Conditions influencing them	• Type of population • Age group • Gender	• Clinical question • Patient category
Information gathered	Being or not being part of the reference population	Patient eligible for a certain procedure ('treatment')
Statistics	95% central range of the distribution curve	ROC curves and predictive values
Data number	Two (lower and upper limits)	One or more, according to the likelihood of clinical situation or different clinical questions

ROC, receiver-operating characteristic

Summary of analytical and biological requirements in the adoption of traceable reference intervals

	Responsibility
Analytical requisite:	
• Existence of a reference system	• IFCC, JCTLM, National Metrology Institutes
• Availability of commercial assays producing traceable results	• IVD manufacturers
• Correct implementation of traceable assays in the clinical setting	• Clinical laboratories
• Control of the performance of commercial assays within stated limits of uncertainty	• Clinical laboratories, EQAS organizers
• Compatible pre-analytical conditions	• Clinical laboratories
Biological requisite:	
• Accurate definition of traceable reference intervals, providing information on the influence of biological and environmental factors	• Joint effort between laboratory profession and IVD manufactures
• Validation of the applicability of the traceable reference intervals to the laboratory's own population	• Clinical laboratories

EQAS, external quality assessment scheme; IVD, in vitro diagnostic.

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Category	Pre-requisite	Responsibility for implementation
Analytical	Existence of a reference measurement system (trueness-based)	IFCC, JCTLM, national metrological institutes
	Existence of traceable routine methods	Manufacturers
	Correct implementation of methods in clinical laboratories	Clinical laboratories
	Control of the performance of routine methods to keep them within stated limits for uncertainty	Clinical laboratories, EQAS organizers
Clinical	Accurate definition of reference intervals, providing information on the influence of biological and environmental factors	Joint effort between IFCC, manufacturers and clinical laboratories
	Comparable preanalytical phase	Clinical laboratories
	Validation of applicability of common reference intervals to the laboratory's own population	Clinical laboratories
	Adoption of common reference intervals	Clinical laboratories

Reference intervals as a tool for total quality management

Special issue: Quality in laboratory diagnostics: from theory to practice

Gian Cesare Guidi, Gian Luca Salvagno*. Reference intervals as a tool for total quality management. Biochemia Medica 2010;20(2):165-72. http://dx.doi.org/10.11613/BM.2010.020

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Neonatal period (1–6 months)
Infancy (6 months–3 years)
Childhood (3–6 years)
Pre-pubertal (6–11 years)
Puberty (11–18 years)
Adulthood (18–45 years)
Pre-menopausal
Post-menopausal
Maturity (45–65 years)
Old age (> 65 years)

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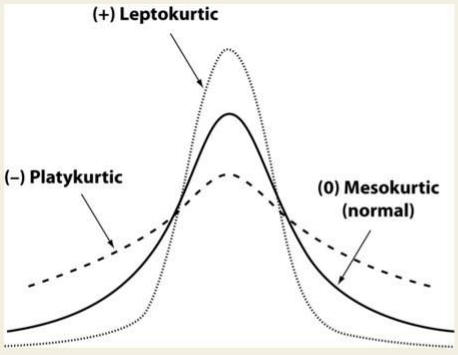

Figure 4. General forms of kurtosis.

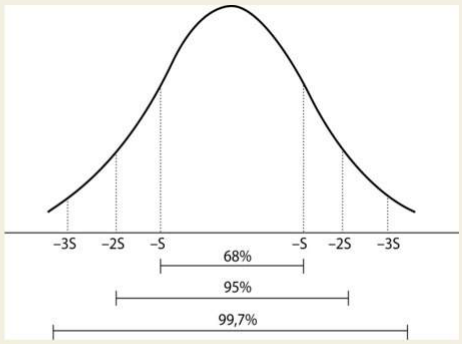

Figure 5. Interval of reference: Gaussian curve.

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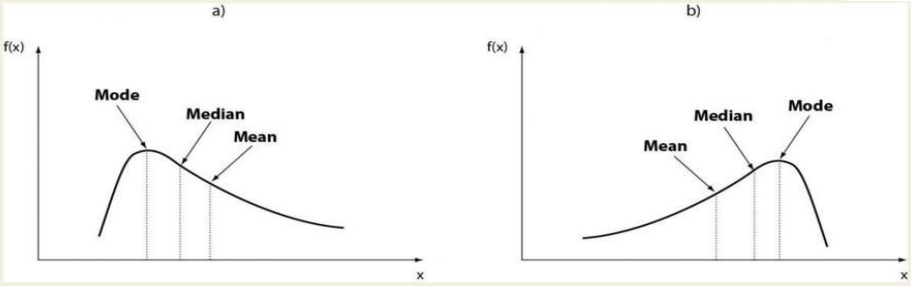

Figure 2. Non-Gaussian distribution (non-normal).

Figure 3. Tendency to asymmetry (skewness).

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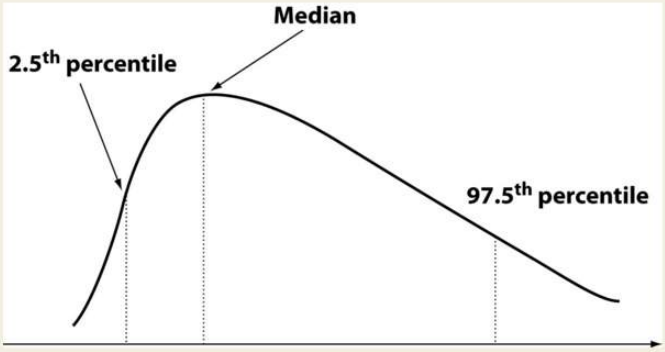
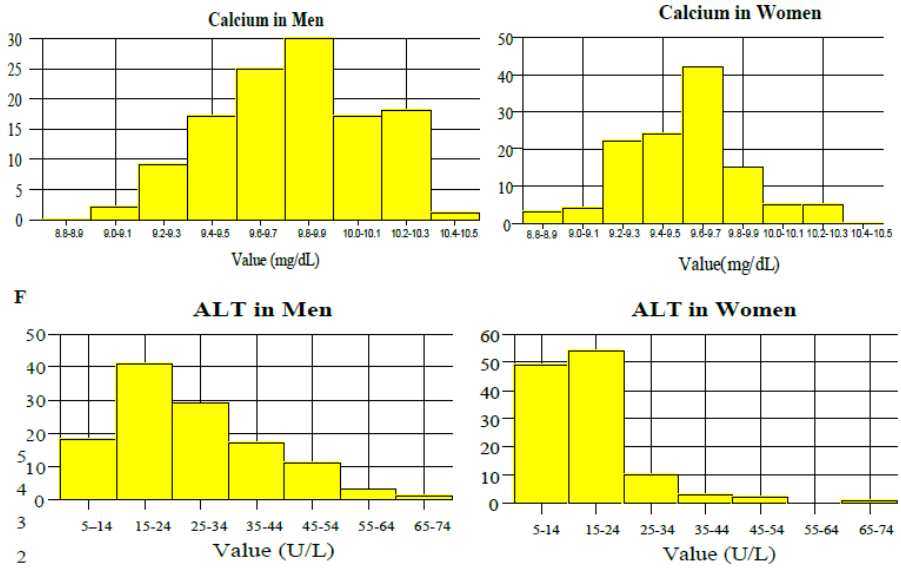


Figure 6. Interpercentile intervals: nonparametric distribution.



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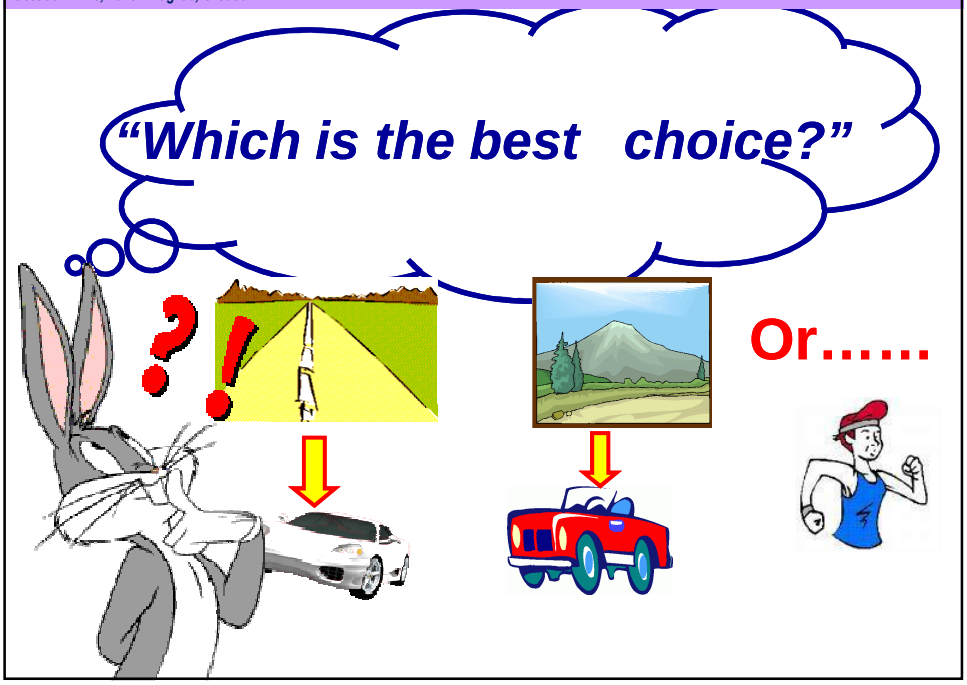
Non-parametric statistical techniques are used to analyze the data not having a specific type of probability distribution. In general, when observing non-Gaussian distributions (non-normal) (Figure 2a-b), their description is assigned to other indices such as median, percentiles classes, and more others. Moreover, in this second category of data distribution, other methods become more useful, including the so called and important ones "bootstrap methods". Sometimes non-Gaussian distributions can be normalized via appropriate processing techniques (12). This is the general case of distributions obtained from experimental data, for which the assumption of normality is always verified. In constructing a reference range from individual data, often the difficulty of achieving a perfect Gaussian distribution is apparent. Even after sampling the data from a population which is presumed to be normally distributed, it is often necessary to take some approximations of the data to comply with the assumption of normality. In this regard a series of statistical tests have been put in place, which compares the distribution of experimental data with a hypothetical Gaussian distribution (13–15). These methods are called mathematical-statistical *goodness-of-fit test* tests. Among them, the most known and used is the Kolmogorov-Smirnov, although its real discriminant power is questioned by some researchers, especially when the parameters of the distribution are estimated based on data rather than being specified *a priori*. Afterwards, other tests have been proposed that are best suited for this purpose, among them the test of Shapiro-Wilks (for distribution of samples greater than 2,000 subjects it should be replaced by the test for normality of Stephen) and the test of D'Agostino-Pearson. None of these tests can however indicate the type of non-normality observed in the case where the distribution is showing tendency to asymmetry (skewness) and kurtosis or both (Figure 3).


"Which is the best choice?"
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EXCLUSION CRITERIA

Alcohol consumption	Illness, recent
Blood donor	Lactation
Blood pressure, abnormal	Obesity
Drug abuse	Occupation
Drugs, prescription	Oral contraceptives
Drugs, over the counter	Pregnancy
Environment	Surgery, recent
Fasting or nonfasting	Tobacco use
Genetic factors	Transfusion, recent
Hospitalization, current/recent	Vitamin abuse

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EXEMPLE OF PARTITIONING FACTORS

Age	Geographic location
Blood group	Posture when sampled
Circadian variation	Race
Diet	Sex
Ethnic background	Stage of menstrual cycle
Exercise	Stage of pregnancy
Fasting or nonfasting	Tobacco use

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PRE-ANALYTICAL FACTORS FOR CONSIDERATIONS

Subject Preparation	Specimen Collection	Specimen Handling
• Prior diet • Fasting vs nonfasting • Abstinence from pharmacologic agents • Drug regimen • Sampling time in relation to biological rhythms • Physical activity • Rest period before collection • Stress	• Environmental conditions during collection • Time • Body posture • Specimen type • Collection site • Site preparation • Blood flow • Equipment • Technique • Tourniquet time	• Transport • Clotting • Separation of serum/plasma • Storage • Preparation for analysis

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What's next?

IFCC Document

Clin Chem Lab Med 2010;48(11):1537–1551 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.319

An appraisal of statistical procedures used in derivation of reference intervals

Kiyoshi Ichihara[1,*] and James C. Boyd[2] on behalf of the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL)

Clin Chem Lab Med 2010;48(11):1593–1601 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.315

Common reference intervals for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) in serum: results from an IFCC multicenter study

Ferruccio Ceriotti[1,*], Joseph Henny[2], Josep Queraltó[3], Shen Ziyu[4], Yeşim Özarda[5], Baorong Chen[6], James C. Boyd[7] and Mauro Panteghini[8] on behalf of the IFCC Committee on Reference Intervals and Decision Limits (C-RIDL) and Committee on Reference Systems for Enzymes

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Clin Chem Lab Med 2004;42(7):692–697 © 2004 by Walter de Gruyter • Berlin • New York

The evolution of the reference value concept

Ralph Gräsbeck*

Minerva Foundation Institute for Medical Research, Biomedicum Helsinki, Helsinki, Finland

Clin Chem Lab Med 2012;50(5):761–763 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/cclm-2012-0089

Editorial

Reference values and the journal: why the past is now present

Mario Plebani and Giuseppe Lippi

Clin Chem Lab Med 2004;42(7):710–714 © 2004 by Walter de Gruyter • Berlin • New York

The IFCC recommendation on estimation of reference intervals. The RefVal Program

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Certification, registration and accreditation

ISO 14001:2004, "certification" refers to the issuing of written assurance (the certificate) by an independent external body that has audited your management system and verified that it conforms to the requirements specified in the standard. "Registration" means that the auditing body then records your certification in its client register.

On the contrary, using "accreditation" as an interchangeable alternative for certification or registration is a mistake, because it means something different. In the ISO 9001:2000 or ISO 14001:2004 contexts, accreditation refers to the formal recognition by a specialized body – an accreditation body – that a certification body is competent to carry out ISO 9001:2000 or ISO 14001:2004 certification in specified business sectors. In simple terms, accreditation is like certification of the certification body. Certificates issued by accredited certification bodies may be perceived on the market as having increased credibility.

Take a home message

- Reference intervals "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" (Ceriotti F. Prerequisites for use of common reference intervals. Clin Biochem Rev. 2007;28:115-121).
- It has been recommended that an Reference Intervals be established by selecting a statistically enough group of healthy people.
- Clinical laboratory professionals, who want to provide a high quality report, should comply with the requests of quality standards like ISO 15189:2012, which specifically asks for a periodical review of biological reference intervals.