Working Group Report

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Determination and verification of reference interval limits in clinical chemistry. Recommendations for laboratories on behalf of the Working Group Guide Limits of the DGKL with respect to ISO Standard 15189 and the Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations (Rili-BAEK)

https://doi.org/10.1515/labmed-2018-0500
Received December 15, 2018; accepted April 10, 2019; previously published online June 1, 2019

Abstract: Laboratory measurement values require interpretative assistance e.g. so-called guide limits (GL), as an interpretative aid. Legal and normative requirements for medical laboratories do not provide specific information for their implementation and verification. A German Society for Clinical Chemistry and Laboratory Medicine (DGKL) Working Group GL (WG-GL) has, therefore, developed recommendations to support medical laboratories in the management of GL. A specific objective was to create a framework that mainly takes into account those aspects that can be realistically implemented by routine laboratories and that should improve the management of GL of frequently requested quantitative measurement procedures in clinical chemistry. Thus, the focus of these recommendations is on the distinction between reference interval limits and clinical decision limits as well as the determination and verification of reference interval limits. Indirect approaches are highlighted, as they enable routine laboratories with a broad analytical spectrum but limited resources to evaluate or to establish reference limits.

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Keywords: accreditation; decision limits; guide limits; indirect methods; ISO 15189; reference intervals.

Brief summary: Recommendations are provided to support medical routine laboratories in the management of guide limits. The distinction between reference interval limits and clinical decision limits allows to focus on aspects that can be realistically implemented for frequently requested quantitative measurement procedure in clinical chemistry. Indirect approaches are highlighted, as they enable routine laboratories to evaluate or to establish reference limits despite limited resources.

Introduction

Laboratory reports require interpretative assistance besides the measurement results. Usually, the attending physician interprets laboratory findings by comparing the reported values with so-called guide limits (GL), a generic term that summarizes different reference classes.

Many authors have pointed out the different prioritization of analytical accuracy and the validity of the corresponding reference values [1–3].

GL are usually taken from the package inserts of *in vitro* diagnostics (IVD) manufacturers or external literature sources. It must be assumed that, despite normative requirements, only a minority of all laboratories systematically practice the evaluation of these data. The situation is currently aggravated by the fact that IVD manufacturers are increasingly pointing out that laboratories are responsible for establishing their own reference interval limits.

Although legal and normative requirements, in particular the Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations (Rili-BAEK) [4] and in part the DIN EN ISO 15189 (ISO 15189; "Medical laboratories – Requirements for quality

and competence") [5], stipulate concrete requirements for internal and external quality assurance measures that ensure the quality level of analytical accuracy, quality assurance of GL is neglected so far.

Paragraph 3.4 of ISO 15189 describes the term "biological reference interval". In paragraphs 5.4.2, 5.5.2, 5.5.3 and 5.8.3, this standard requires their documentation, use and regular verification. Paragraphs 6.2.3 and 6.3.2 of the Rili-BAEK [4] oblige laboratories to provide reference interval limits of healthy individuals. The source and all actions performed concerning their GL provided on laboratory reports must be documented.

Thus, the availability and use of adequately chosen reference interval limits are mandatory for all medical laboratories.

The following sections describe minimum requirements and recommendations for accredited laboratories that focus on the definition, establishment and verification of reference interval limits. The specific aim of our recommendations was to create a framework that only considers those aspects that can be realistically implemented by routine laboratories and that are suitable to significantly improve the handling of GL in the field of clinical chemistry.

Clinical decision limits are explicitly not considered in the following recommendations. However, definitions for both reference interval and clinical decision limits are provided in order to allow a clear distinction. A laboratory self-assessment checklist is provided as supplementary material.

Definition of guide limits

Different entities are summarized under the generic term guide limits. Nomenclature and classification at both the national and international levels have not yet been harmonized. ISO 15189 generically defines reference interval as the distribution of values taken from a biological reference population that is in general the central 95% range. No definition is provided for clinical decision limits. Accordingly, requirements obliged by ISO 15189 do not clearly distinguish between clinical decision limits and reference interval limits, although this is crucial for the actions to be taken by the laboratory. Therefore, the laboratory must initially assess whether the information provided by the manufacturer or sources represent reference interval limits or belong to another class of clinical decision limits. Basically, four types of GL can be distinguished as proposed by the Working Group GL (WG-GL) [6, 7] and illustrated in Figure 1.

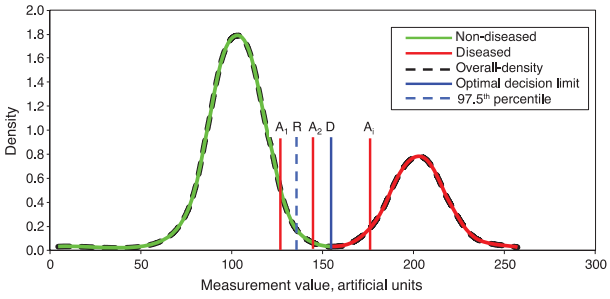

Figure 1: Theoretical distribution of measured values of "healthy" subjects and patients with various GLs.
Upper reference limit (R): the 97.5th percentile of a reference population (95% of all non-pathological patients), unimodal consideration. Upper decision limit (D): separates a non-pathological from a pathological group (point of intersection of the two distribution functions). The maximum diagnostic efficiency in bimodal consideration is given at the theoretical decision limit. Action limits (A1-i): expert groups recommend when a diagnostic or therapeutic action should take place (empirical decision limit, e.g. 200 mg/dL total cholesterol or 126 mg/dL [7 mmol/L] glucose). Solid green line: non-diseased subjects; solid red line: diseased subjects; dashed black line: overall density function.

Reference interval limits

Lower and upper reference interval limits describe the central 95% reference interval of measured values obtained from samples of a "healthy" reference group (non-pathological with respect of the measurand). As a convention, 2.5% of the values are below and above the reference interval limits.

Clinical decision limits

Empirical decision limits

Empirical decision limits identify individuals with a specific risk that requires further diagnostic or therapeutic steps (also called action limits); they are determined in clinical studies or as a result of clinical experience and are usually stated by consensus groups. Examples are the limit 200 mg/dL (5.2 mmol/L) total cholesterol or 126 mg/dL (7 mmol/L) glucose.

Theoretical decision limits

Theoretical decision limits should be distinguished from empirical decision limits as there are considerable differences concerning their characteristics or intended purpose, respectively.

As empirical decision limits may also rely on risk-based, financial, ethical or other issues, the specific characteristic of theoretical decision limits is to indicate the concentration with the maximum diagnostic efficiency. Theoretical decision limits mark the concentration with the smallest overlap between diseased and non-diseased individuals and therefore may also be seen as the optimal decision limit with regard to its power to separate both populations (Figure 1).

Therapeutic intervals

Therapeutic intervals define the optimal concentration interval of therapeutic drugs and help to distinguish between subtherapeutic, therapeutic or toxic concentrations.

Contrary to reference interval limits (unimodal consideration), clinical decision limits consider both the distribution of measurement values from "healthy" persons and patients (multimodal consideration).

Critical values (also called "panic values") are not classified as GL. Critical values trigger an accelerated transmission of diagnostic findings. These limits are individually negotiated between clinicians and laboratories and are therefore extremely variable [8].

Forensic limits (as e.g. for ethanol to assess the fitness to drive) were also not considered as well as decision limits used in the fields of occupational or environmental medicine [9, 10].

Differences between reference interval limits and empirical decision limits

Table 1 summarizes the characteristics that distinguish reference interval limits from empirical decision limits. In contrast to reference interval limits, prerequisites for the implementation and verification of clinical decision limits do not appear to be feasible for routine laboratories. They can neither recruit appropriate clinical populations with defined outcomes nor adjust clinical decision limits to specific preanalytical or analytical conditions of the respective laboratory or locally served patients. In addition, clinical decision limits are often defined by expert consent and are therefore hardly objectively verifiable by routine laboratories.

Procedures for estimating reference interval limits

Reference intervals were traditionally estimated by *direct* approaches derived from "healthy" individuals. Selection criteria are applied *a priori* as the most common study design to define the reference population, or these criteria are applied after the measurement results have been obtained in a so-called *a posteriori* approach. *Indirect* approaches rely on routine clinical pathology databases.

Whereas direct approaches use only one distribution of measurement values from a non-diseased subpopulation, indirect methods are based on values from a mixed distribution including values from diseased subjects (data mining). A major criterion to be considered with indirect methods is whether there is a need to distinguish between data from stationary patients (hospitals' inpatients) and primary care patients (outpatients recruited from hospitals and doctor's practices). Both direct and indirect methods may collect data from multiple centers (applying the same analytical procedures) in order to overcome problems with low sample sizes or to achieve common reference interval limits.

Statistical concepts on the determination of reference interval limits by direct methods comprise a proper

Table 1: Comparison of empirical decision limits and reference interval limits (modified according to Ozarda et al. [11]).

Issue	Reference interval limits	Empirical decision limits
Number of values	Statistical limits (two values)	Clinical threshold (usually one value)
Derivation	A biological characteristic of the "healthy" population	A decision regarding a specific clinical situation, requires a "healthy" and a second subpopulation with a specific disease
Based on	95% central interval of the reference distribution	Clinical outcome studies, guidelines and consensus values, ROC curves
Defined by experts	Laboratory experts	Clinicians and laboratory experts
Transparency of estimation	Easily available	Difficult to retrace

ROC, receiver operating characteristic.

sample size calculation. The probability distribution of the measurand in the reference population determines whether further data modulation steps, such as log-transformation, are necessary or whether parametric or non-parametric statistics are employed, respectively, to determine a central 95% reference interval.

The crucial challenge of *indirect* approaches is the isolation of a non-diseased subpopulation (for review see Haeckel et al. [1]). Graphical methods [12, 13] are still in use, but especially those that include subjective steps by the operator may be seen as obsolete. More sophisticated algorithms are utilized in the Reference Limit Estimator software [14–16].

Benefits and disadvantages of direct and indirect approaches for estimating reference intervals

Laboratories have to decide whether direct or indirect methods are applied in order to implement or verify reference interval limits. Table 2 summarizes various aspects that shall be considered. The main advantages of direct methods are that they are applicable to a broader analytical spectrum and may still have a higher standing, even though amended International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommendations have included indirect methods [17]. Indirect methods, in contrast, provide substantial benefits in particular as regards their practicability.

Recommendations for the implementation and verification of reference intervals

The need to define or verify reference intervals exists whenever a quantitative measurement procedure is introduced, replaced or modified. Verification is also necessary if there is evidence that the existing reference intervals have not been adequately chosen or that they no longer reflect the reference population.

In the case of missing, incomplete or inapplicable manufacturer information, the laboratory may use the information from other sources to report preliminary reference interval limits. The preliminary status of these reference intervals shall be indicated on the laboratory report. The underlying sources must be documented by the laboratory and made accessible to the customer in an appropriate way.

The Clinical and Laboratory Standards Institute (CLSI) Evaluation Protocol (EP) 28-A3c [19] recommends that nationally or internationally approved decision limits should be preferred to reference intervals. The report shall also include the underlying source of decision limits.

Table 2: Comparison of direct (by selected subjects) and indirect methods (by data mining) for reference interval determinations (modified according to Haeckel et al. [1] and Jones et al. [17]).

Issue	Direct	Indirect
Experimental work	Considerable	Not required
Statistical performance	More easy	Requires more expertise, some methods require subjective assessment
Stratification	Difficult to get spread of subjects by age and sex	Spread of ages and sex already available
Reference population	“Healthy”	Match the clinical use of the test
Defining “health” status	Difficult	Not required
Preanalytical conditions	May not match routine conditions	Match routine conditions
Analytical conditions	May not match routine conditions	Match routine conditions
Economic impact	High	Not relevant
Repeatability of the study	Difficult	Easy
Ethical issues	Must be considered (selection of reference samples, consent of ethical commission)	Not existent[b]
Transference and verification	More difficult	Easy
Required number of samples	≥120	Not yet established[a]
Support of quality assurance	Not possible	Can be easily implemented

[a]Usually higher numbers are used because they are readily available. Therefore, indirect reference intervals have lower confidence intervals (see Haeckel et al. [18]). [b]If the data are collected anonymously and cannot be traced back to specific individuals.

Laboratories that apply in-house assays have to comply with the "General Safety and Performance Requirements" according to Annex I of the IVD Regulation (EU) 2017/746 [20]. Laboratories shall use direct methods in all cases of newly developed measurement procedures if there is no opportunity to transfer reference interval limits from existing sources.

As soon as a sufficient number of representative laboratory results are available, the laboratory has to check whether there are relevant differences between the preliminary limits and internally estimated reference interval limits (see Section "Verification of reference intervals").

The quality management system of a laboratory has to establish schedules for the regular review of its reference intervals. The planning shall include deadlines (e.g. 4 years) after which an established reference interval must have been reassessed at the latest. The result of the reassessment must be documented.

It is assumed that according to German legal obligations, the approval of reference intervals before introduction or after modification as well as the evaluation and approval of reports about the verification of reference intervals are medical tasks that cannot be delegated to non-medical personnel [21].

Verification of reference intervals

Paragraph 5.5.2 of ISO 15189 stipulates the periodical verification of reference intervals but does not provide further specifications [5]. The reported reference intervals must be verified under routine conditions to confirm their validity in the specific setting of the respective laboratory.

The transferability of currently used reference intervals in case of an exchange or modification of the measurement procedure is also referred to as verification in this context [22].

Verification encompasses both (i) an initial plausibility check as well as (ii) experimental investigations if a sufficient amount of data is available.

Plausibility check of reference intervals selected from external sources

The manufacturer's information on reference intervals should be crosschecked with or extended by independent sources if necessary. Applicable sources may include primary literature or reference interval records obtained from other laboratories.

Manufacturer's information as well as all sources used instead of or in addition to the manufacturer's information must be evaluated with regard to their transferability to the measurement procedure used and assumed reference population of the laboratory.

The *reference collective* given by the manufacturer or from external sources has to be evaluated in particular with regard to the transferability of age, gender, ethnic homogeneity and type of recruitment protocol (e.g. blood donors, outpatient or inpatient care, etc.) [7, 23, 24].

The transferability of the *measurement procedure* must be evaluated with regard to quality, starting with pre-analytical aspects, methodological differences and possible further factors that may impair comparability.

The mathematical/statistical model used to determine the reference interval limits shall also be taken into account.

Experimental investigations

Various methodological approaches are described for the experimental determination and verification of reference intervals, using both direct and indirect methods (for further details see Haeckel et al. and Jones et al. [1, 17]).

Direct methods

Direct methods require, in general, at least 120 healthy reference individuals to establish new reference intervals [19]. However, such a relatively small number leads to broad confidence limits [18]. A minimum of 20 healthy individuals is recommended to verify existing or preliminary reference intervals [19]. If age and/or gender dependencies or other relevant biological factors are known [25], this amount of well-characterized healthy individuals should be recruited for all subsets (partitions), e.g. the respective age groups, both sexes or other instances such as pregnancy, and all of these should be verified periodically. Due to these multipliers, the use of direct methods to determine new reference intervals and subsequently verify established or preliminary reference intervals is rarely feasible in medical laboratories with broad analytical spectra.

Indirect methods

Indirect methods are of particular interest to routine laboratories as they allow the determination and verification of reference intervals from existing laboratory data sets [1, 17].

A further benefit of indirect methods is the establishment of reference intervals if dynamic age dependencies occur.

Several approaches have been developed to determine indirect reference intervals and are meanwhile accepted as a valid alternative to direct methods [1, 17].

The Reference Limit Estimator software [14–16] developed by the WG-GL is available free of charge to medical laboratories for this purpose (https://www.dgkl.de). The implemented algorithms also allow a comparative evaluation with existing reference intervals (see Section "Comparability of reference intervals).

Recently, some providers of laboratory information systems have launched software extensions which have integrated the algorithms of the Reference Limit Estimator software into their data processing routines or offer interfaces which enable the export, re-import of the resulting reference intervals and their controlled transfer into the master data of laboratory information systems.

Currently, the Reference Limit Estimator software can only be applied if a sufficiently large number of measured values are available. This limitation can partly be circumvented by pooling data from several laboratories (prerequisites see Section "Procedures for estimating reference interval limits").

Comparability of reference intervals

Reference intervals derived from external sources or determined by the laboratory itself or resulting from their verification may show more or less pronounced differences [26, 27]. These differences may be due in particular to factors, such as

(i) differences between populations,
(ii) preanalytical influences,
(iii) differences between measurement procedures,
(iv) statistical methods used,
(v) intraindividual variations or
(vi) uncertainty of measurement of a measurement procedure.

The laboratory has to assess the relevance of such differences on the basis of experience and scientific literature, taking into account the aforementioned or other factors if applicable. The comparison of data sets from different laboratories with comparable measurement procedures and reference populations and pre- and post-analytical methods based on the same standards may also be used for verification as well as data from verification or validation of measurement procedures such as method comparison studies [22].

Evidence can be supported by means of the permissible limits for imprecision of measurement [26, 28]. The necessary calculation steps are implemented in the Reference Limit Estimator software.

Conclusions

Minimum requirements and recommendations are proposed for accredited laboratories that focus on the definition, establishment and verification of reference interval limits. A checklist is provided as supplementary material that can help to systematically assess compliance with ISO 15189 and also contains requirements that have been consented within the WG-GL as essential and practically feasible.

The Reference Limit Estimator software is a useful tool to overcome limitations of formerly reported indirect approaches to determine reference intervals. It enables routine laboratories to establish and verify reference intervals for quantitative measurements, especially those with high throughput.

Direct approaches are required whenever indirect methods cannot be applied. A realistic assessment of the current possibilities of routine laboratories, however, shows that a *lege artis* implementation of EP28-A3c exceeds the resources of many of these laboratories. The same obstacles apply to the establishment and review of clinical decision limits. It would require close collaboration between laboratories and clinicians and additional resources that are not covered by current reimbursement structures.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/labmed-2018-0500).