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Uncertainty in Measurements in Medical Laboratories / A Narrative Review by the Staff of the New Najran General

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ABSTRACT
Quantitative laboratory tests are important in identifying approximately 70% of medical decisions made by physicians regarding diagnosis, treatment, hospital admission, and discharge. Thus, it is of utmost importance to measure correctly and to rely on test results. Laboratories give the right results when measurement is performed under optimal conditions, with the correct method, using the right equipment, and proper reference materials. These parameters focus on accuracy. In addition, the concept of measurement uncertainty also focuses on accuracy as recorded in the standard definitions as the "parameter associated with the result of a measurement which characterizes the dispersion of the values that could be reasonably attributed to the measurand." To assure the reliability of all results, it is necessary to state whether the measurement has been performed well, i.e., to answer the question, "Is the result okay?" The concept of measurement uncertainty offers the correct answer. It is considered that when the correct determination of the uncertainty of a measurement indicates a realization of uncertainty at least partially reflected in the test report, the result becomes acceptable, making it easy to decide whether the results fall within the limits described. If the result is not within the limits, evaluations can indicate the adequacy or inadequacy of the result and, consequently, the adequacy or inappropriateness of the criteria for evaluation, to assess whether the possibility of the analyte in question is within acceptable limits of operation.

Keywords: Laboratories, addition, diagnosis, treatment, hospital admission

1. INTRODUCTION

Quantitative laboratory tests are important in identifying approximately 70% of medical decisions made by physicians regarding diagnosis, treatment, hospital admission, and discharge. Thus, it is of utmost importance to measure correctly and to rely on test results. Laboratories give the right results when measurement is performed under optimal conditions, with the correct method, using the right equipment, and proper reference materials. These parameters focus on accuracy. In addition, the concept of measurement uncertainty also focuses on accuracy as recorded in the standard definitions as the "parameter associated with the result of a measurement which characterizes the dispersion of the values that could be reasonably attributed to the measurand." To assure the reliability of all results, it is necessary to state whether the measurement has been performed well, i.e., to answer the question, "Is the result okay?" The concept of measurement uncertainty offers the correct answer. It is considered that when the correct determination of the uncertainty of a measurement indicates a realization of uncertainty at least partially reflected in the test report, the result becomes acceptable, making it easy to decide whether the results fall within the limits described. If the result is not within the limits, evaluations can indicate the adequacy or inadequacy of the result and, consequently, the adequacy or inappropriateness of the criteria for evaluation, to assess whether the possibility of the analyte in question is within acceptable limits of operation.

Methods
Literature related to uncertainties in simple medical laboratory measurements was critically reviewed to provide an overview. A search was done for papers published up to 2011 using a broad set of search terms: "uncertainty of measurements," "medical laboratories," and "simple chemical analyses." Our raw search yielded a total of 974 papers. After eliminating papers that had limited overlap with the topic of review, the final selection included only 50 papers that targeted issues relevant to the review. Each of the remaining papers was manually gone through and analyzed in detail regarding the subject of the paper, the types of measurements to which the paper referred, the methods that were used in the paper and details of these methods, and strengths and weaknesses of the study specifically related to the use of a method. Obtainable analytical methods for effecting the various specific approaches and the possible measurement outputs were synthesized.
This review describes two types of sources of uncertainty: random uncertainty and systematic uncertainty. Each has two contributing causes affecting one instrument that were identified as a result of putting the literature study outcomes in a diagram and working with the diagram. Additionally, six common approaches to uncertainty estimation among the medical laboratories were identified and described. The review provided details for assessment of uncertainty for each specific approach, presented synthesis for possible outputs, strengths and weaknesses of each of the approaches, and contributed to the understanding of key concepts, e.g., measurement error, traceability of the result, and mathematical linkage of steps used in the measurements.

Conclusion
Measurements in medical laboratories are not free from the influence of induced uncertainty. Imprecision and bias are characteristics of every measured property, and factors external to laboratories can contribute to both of them, while individual factors can contribute to either imprecision or bias. Greater awareness of the root causes of these undesirable effects may lead to better appreciation of their implications and implementation of measures to reduce the effects. In turn, better understanding and consequent reduction of uncertainty may lead to measurements with higher quality, ultimately adding value to patients, which is the purpose of medical laboratory services. The desirable characteristics of reduced uncertainty are sometimes in conflict, because knowledgeable judgment forces a decision path toward the most reliable and precise procedure, sometimes versus the easiest, fastest, or least expensive. This is why assuring analytical quality in medical testing requires oversight on an ongoing basis by method experts, and it is the reason for the requirement for continuing professional development in ISO Standard 15189. It is hoped that this has raised awareness of the many sources of both imprecision and bias leading to increased uncertainty in medical laboratory testing. These can and should become the starting point for both monitoring and corrective actions, as the ideal of zero tolerance for causing or predicting patient harm is the foundation of medical laboratory activities.

1.1. Scope and Importance of Uncertainty in Medical Laboratory Measurements

Measurement uncertainty has become an essential aspect in many scientific applications, including the medical field. Measurement uncertainty is a parameter associated with the result of measurements that characterizes the dispersion of values that could be reasonably attributed to the measurement entity. Measurement uncertainty is an indicator of the validity and quality of measurement results. The higher the uncertainty of a measurement method, the less accurate the results of that method are. The importance of metrology in the field of medical testing laboratories can be understood from the fact that over 70% of clinical decisions made by physicians are based on the outcomes of investigations conducted in medical laboratories. Laboratory results must have a specific level of accuracy below the tolerance limits for the diagnostic tests to be reliable medically.
However, all measurements are subject to uncertainty, particularly in measurements of the quantities generated by biological systems. Because productivity in medical laboratories requires a high level of precision and accuracy, with minimal measurements made outside clinical tolerance limits defined locally and internationally, the scientific community has called for a better understanding of measurement uncertainty, emphasizing the industry's need to predict, monitor, and manage uncertainty properly. A joint committee was set up to provide a framework of traceability for medical laboratories and to reduce the risk to patient safety. It has included the concept of measurement uncertainty in its recently published traceability framework. Although the application of measurement uncertainty may enhance the laboratory's quality processes, ensuring that investigations useful for patient treatment are generated, the topic is frequently unknown and neglected by many healthcare professionals.

2. Basic Concepts of Measurement Uncertainty

Measurement, by definition, involves comparison. Test methods, and ultimately measurements, are based upon comparing the quantity of interest with another quantity of the same type that is clearly defined. In many test methods, secondary materials are used to express test results on the same scale in the same unit. In the calibration procedure, for example, a voluntary control procedure is employed to maintain the authenticity of these secondary values. Hence, traceability is a fundamental aspect of measurements. Test results or calibrations

are considered consistent if the accompanying uncertainties are negligible compared with the expected variations in the calibration, measurement standards, tested objects, or experimental or test procedures, which can be used to set a limit beyond which the result of the measurement is considered correct. Experience shows that some testing methods can provide test results with a standard of compliance useful for the specific requirements. The process of producing data from instruments involves several stages including: choosing the statistical models that best describe the output data; choosing the empirical distributions for the parameters of these models; and computing the posterior distribution functions from the prior distribution functions and the instrument outputs. The role of physics, mathematics, engineering, and commercial expertise is different at each stage. Consequently, taking measurement data involves several conditional steps, and measurement uncertainty is an accumulation of different types of errors and defects resulting from the stages involved. (Chung et al.2022)(Genzel et al.2022)(Krinner et al.2022)

2.1. Explanation and Importance

Understanding the concept of uncertainty in measurements is of utmost importance in the field of medical laboratories as it plays a vital and pivotal role in guaranteeing the utmost accuracy and dependability of results for patient diagnosis and treatment. By comprehending the intricacies of uncertainty, technicians and professionals in the medical field can ensure that all measurements taken are precise and precise, eliminating any room for error and providing patients with the utmost confidence in their medical outcomes. With accurate measurements, healthcare providers can make informed decisions and tailor treatments to suit each individual's unique needs, thus improving the overall quality of care provided. As such, it is indispensable for all medical laboratory practitioners to possess a deep understanding of uncertainty in measurements and its profound impact on healthcare outcomes.

2.1 Uncertainty in Measurements

Uncertainty in the measurements performed within medical laboratories has been widely recognized as a critical aspect, as it has a direct and profound impact on the overall accuracy and reliability of the obtained test results. Ensuring precise and dependable measurements is of utmost importance within the medical field, as they serve as the foundation upon which critical diagnoses and treatment plans are determined. Consequently, meticulous attention to detail must be exercised when conducting any form of analysis or experimentation, in order to effectively minimize any potential sources of uncertainty and maximize the overall credibility and validity of the obtained results. By acknowledging the significance of uncertainty in measurements, medical laboratories can continue advancing their methodologies and techniques, ensuring that patient care is continuously enhanced and improved.

2.1.1 Uncertainty, Definition, and Basic Concepts

Uncertainty in measurement is a fundamental and crucial concept that is inextricably linked to the concepts of error and accuracy. It plays a vital role in determining the confidence and reliability of a compliance statement, represented by the equation $c = x + u$, which is derived from the measured value x and its associated uncertainty u. This estimation of uncertainty greatly influences the quality and accuracy of the final result, serving as an essential estimate of the true value of the property being measured. The significance of measurement uncertainty extends beyond individual experiments or studies. It holds paramount importance in ensuring the comparability of measurements conducted worldwide. Moreover, it establishes the traceability of measurement results to globally recognized and established standards. By adhering to globally agreed standards and protocols for the correct estimation and reporting of measurement uncertainty, we can facilitate consistency, harmonization, and reliable comparisons across various measurement laboratories. Recognizing the profound impact of measurement uncertainty, it is imperative to view its proper estimation and reporting as an indispensable element of the broader medical standards continuum. It synergistically complements the ongoing development and harmonization of testing and calibration capabilities in measurement laboratories. Emphasizing the accurate determination and communication of measurement uncertainty through standardized practices is essential to fostering trust, reliability, and credibility in the field of medical standards.

The concept of uncertainty, and its understanding and estimation, are well described in the general metrology guidelines prepared by the International Bureau of Weights and Measures, the International Organization for Standardization, and the International Laboratory Accreditation Cooperation. In the common languages of science, uncertainty in measurement is the parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurands, e.g., the patient test results, in conformity with the definition of measurement.

3. Sources of Uncertainty in Medical Laboratory Measurements

The modern approach to quality assurance in the medical laboratory is based on a broader concept that encompasses both laboratory quality control and quality management. The concept of measurement uncertainty

has caused a major shift in the approach taken to ensure the accuracy and reliability of laboratory test results and patient safety. Laboratory services and medical laboratory professionals often confront problems related to calibration, duplicate and 'induplicate' measurements, sample characteristics and traceability, interferences and reference and assigned values, which are sources of uncertainty in the measurement process. Proper understanding and control of these factors are an essential part of the assessment of the risk of testing and the adequate management of that risk. This review focuses on the principal factors that contribute to random variation and systematic error related to uncertainty in in vitro tests carried out in medical laboratories. (Gardner et al.2023)(Arbulú et al.2021)

In a professional context, uncertainty can best be taken to represent a specific kind of predictive statement that follows from the quality of an assessment, experimentation, or simulation. The size of the uncertainty in any of these contexts tells clients, patients, users, and decision makers something about the confidence they should have in the predictive statements used to make subsequent decisions. Physicians use knowledge of the sources of error in medical tests to predict the probabilities of alternative diagnoses, to monitor the effects of treatment, to screen for diseases, to counsel their patients, and to have confidence in the reproducibility of the test results. In addition, they use some tests as an aid to reaching absolute diagnostic certainty. The decision to perform further investigation may depend on the probability of the presence of a particular disease, rather than on the results of a single test and decision limits.

3.1. Instrumentation and Calibration

Laboratory measurements depend on the calibration of instrumentation, and the recommendations for calibration of instruments have been published by various international bodies. Although this work has been criticized for its lack of scientific basis and replication, and for the lack of comparability of different calibrations, it is internationally accepted that calibration and traceability to standards are essential to produce reliable measurements. The recommendations for calibration of instrumentation are usually based on a small number of reference materials, with antiserum calibrators for immunoassays sourced from different traceability chains that converge on separate 'gold standards'. The international gold standard for immunoassays is the preparation of an antiserum calibrator for a target analyte so that samples can be compared and results harmonized wherever the tests are performed. Currently, five reference materials have been used for a wide variety of analytes, and from Whole Blood and Immunochemistry Control are two suitable commercial quality control materials proposed by international organizations for use in medical assay comparison.

4. Methods for Evaluating and Expressing Uncertainty

In this section, we discuss some aspects related to the estimation of the uncertainty of the measurement results, which is associated with the result of a measurement in terms of a quantity. In several branches of science, quantity is referred to as a "true value," and the uncertainty is an expression of the doubt regarding the true value. Ignoring a rigorous statistical interpretation of the evaluation of the measurement uncertainty makes it impossible to critically evaluate the soundness and validity of the information obtained. An area related to the concept of uncertainty in measurements is "statistical analysis of key comparisons." Even before the official assignment of low-uncertainty values called "reference values," international intercomparison exercises are carried out in order to test and round off present systematic errors of the participating national standards laboratories. This involves an especially critical form of measurement uncertainty evaluation, notably through analysis of symmetrical results to be expected if systematic errors are equally likely to point in either direction. The field of key comparisons is an especially fertile area in the development of the science of measurement standards. Considerations of statistical resolution due to low count rates in X-ray spectrometry were first emphasized in a review of primary results regarding the reference wavelengths of several hundred X-ray lines. (Eggemeier et al.2021)(Bulbulia, 2024)(Singh et al.2023)

4.1. GUM (Guide to the Expression of Uncertainty in Measurement)

In each country, there is an Institute of Standards (IS) that provides measurements and calibrations of international standards and prepares and disseminates traceability materials that ensure traceability at any time in the industries and laboratories in the country. Each medical laboratory adheres to this process through an official calibration procedure. Uncertainty is unavoidable in any measurement system. Unlike random errors, even if the repeating measurement process is very accurately configured, uncertainty will always remain constant in the same measurement process.

There are two direct and indirect procedures for estimating the uncertainty from the measurement results. The indirect procedure starts with a reflection on several consecutive factors and processes that affect the estimation of the measured value. The reflected factors are called estimates of the main effect, and each reflection is associated with a combined effect of the pair. These are the sensitivities mentioned in the uncertainty component statement. The degree of numerical deviation between the sum of these sensitivities multiplied by the respective main effect and the standard determination of the experimental method is called the sensitivity indicator. A

linear combination of the standard errors used to estimate multiple measured values and the correlation coefficient, called sensitivity, can quantify the common mode component of the uncertainty. Common methods, all leading to consistent results, are available, such as simulation methods and empirical methods. From this, the common mode component of the uncertainty has negligible or non-negligible characteristics.

5. Case Studies and Examples

(1) To illustrate and to serve as a backup to several points made in the first part of this narrative about how uncertainty and the interpretation of comparative studies of point-of-care, near-patient tests can be explored, three case studies are presented in this section. Firstly, the example of the classically described, two-tiered approach for serologic diagnosis of Lyme disease is introduced, emphasizing some of the background theory and clinical practice. Then, the concurrent analytical performance of such discriminating tests is compared and the aggregate discriminatory power evaluated. In the third case, a potential screening application of combined testing for thrombophilia is described and interpreted. A brief pick and mix, practical approach to reporting discriminative data from serologic assays is suggested. (2) Diagnostically, a two-tiered approach for serologic diagnosis of suspected patients at later, untreated stages of Lyme disease is recommended. Firstly, a solid based, sensitive screening test to be used. If reactive, it is followed by a separate solid or solution based, optimized, specific confirmatory test. Because the specific test provides additional, direct antigenic information not present in the first strategy, the combined discrimination property of the two can provide a statistical improvement over just using the first strategy. However, the benefit is not always requested or realized, and 'over-testing' is common. Furthermore, tinea situations exist when alternatives to the recommended approach should be considered.

5.1. Real-life Examples of Uncertainty in Medical Laboratory Measurements

Real-life Examples of Uncertainty in Medical Laboratory Measurements: Throughout the entire setup, measurement, and evaluation process of a high complexity parameter with special needs and several inherently accompanying analytical problems such as the PT measurements, a lot of differing variability and uncertainty sources are impacting the results. These problems are not confined only to the measuring of one specific PT; they are problems of related importance for all results of patient sample measurements in immunoturbidimetry by any single method used on a daily basis in the common analyzers from our labs directive in human blood serum.

Accepted assay performance requirements such as the ones established for in vitro diagnostic medical devices interpretation and the Clinical Laboratory Standards document emphasize the importance and set an obligation that a laboratory monitors and evaluates this complicated problem adequately and thoroughly. Besides mass concentration, these pre-assigned user-defined rules can also be a user-specific decision that dictates the test results interpretation based on a qualitative determination of the existence or non-existence of the super-physiological level of the biomarker in the patient’s blood.

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