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RESEARCH AND APPLICATION OF LABORATORY MEDICINE REFERENCE MEASUREMENT SYSTEM

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Abstract: The construction of laboratory medicine reference measurement system is an important guarantee for the traceability of medical laboratory test results, and is also an important basis for achieving standardization and mutual recognition of results. Over the past half century, a laboratory medicine reference measurement system structured around reference measurement procedures, reference materials and reference measurement laboratories has been basically formed and gradually improved. In the past 10 years, the development of China's medical reference measurement laboratories has made significant progress, but the research on reference measurement procedures and reference materials lags behind. The six papers published in the special topic "Research and Application of Reference Measurement Systems in Laboratory Medicine" respectively deal with standardization of clinical chemistry, establishment of reference measurement procedures and uncertainty assessment, development of reference materials and evaluation of matrix effects, and the application of reference measurement systems in in vitro diagnosis. Products (IVD) and applications in laboratory quality evaluation are introduced, hoping to provide reference for further promoting the research and application of Chinese medical reference measurement systems.
Keywords: Measurement system; Measurement procedure; Material; Measurement laboratory

1 OVERVIEW OF THE REFERENCE MEASUREMENT SYSTEM

In laboratory medicine, the purpose of testing human samples is to issue test result reports that can help clinical diagnoses of diseases, assess disease risks, and make treatment decisions. Regardless of the measurement procedure used, the results of samples tested using different in vitro diagnostic products (IVDs) in different laboratories should be equivalent so that each laboratory uses uniform medical decision limits and references. interval to reduce medical decision-making errors caused by unequal test results. One of the important methods to achieve equivalence of test results is to establish and ensure the traceability of test results. The International Joint Committee on Traceability in Laboratory Medicine and the International Organization for Standardization recommend paths and methods to solve the traceability of test items by publishing reference measurement procedures and standard guidelines for test items.

Metrological traceability is the property of a measurement result linking it to a reference object through a documented, unbroken chain of calibrations, with each link point contributing to the measurement uncertainty. The new version of ISO 17511 lists six major categories of calibration level models and charts the currently achievable traceability paths for testing items.

The reference measurement system, also known as the reference system, is an important basis for the measurement traceability of routine test results in clinical laboratories. It mainly consists of reference measurement procedures, reference materials and reference measurement laboratories. A reference measurement procedure, also known as a reference method, is a measurement procedure that has been thoroughly analyzed and studied and produces values with a measurement uncertainty commensurate with its intended use, in particular to evaluate the correctness of other measurement procedures measuring the same quantity and to characterize reference materials hour. A reference material is a substance whose properties are sufficiently homogeneous and stable that it has been determined to be suitable for the intended use in measurement or examination of nominal properties. A reference measurement laboratory, also known as a reference laboratory, is an accredited laboratory that runs reference measurement procedures and provides uncertainty results.

The International Organization for Standardization has released a series of standards and guidelines to clarify the relevant requirements for reference measurement systems, and has continuously improved them in practice. Our country basically adopts the standards issued by the International Organization for Standardization in order to be consistent with the international standards, such as GB/T 19702-2005 "Description of Reference Measurement Procedures for the Measurement of Biological Samples of In vitro Diagnostic Medical Devices" (equivalent to the ISO 15193 standard [2]), GB/T 19703-2020 "Requirements for the content of certified reference materials and supporting documents for the measurement of biogenic samples in in vitro diagnostic medical devices" (equivalent to the ISO 15194 standard [3]), GB/T 27025 —2019 "General Requirements for Testing and Calibration Laboratory Capabilities" (equivalent to ISO/IEC 17025:2017, IDT[4]) and "Calibration Experiments Using Reference Measurement Procedures in Laboratory Medicine" which is being revised in accordance with ISO 15195:2018[5] Room capacity requirements" etc.

In 2002, three major organizations, the International Bureau of Weights and Measures, the International Federation of Clinical Chemistry and Laboratory Medicine, and the International Cooperation for Laboratory Accreditation, jointly

established the JCTLM to guide and promote world-recognized equivalent measurements in laboratory medicine and trace the origin of laboratory medicine measurement standards. Provide a global platform. JCTLM Working Group 1 is responsible for the database review of reference measurement services; Working Group 2 is responsible for the promotion and education of measurement traceability to reduce methodological differences, improve clinical results and patient safety; Working Group 3 is responsible for evaluating the completeness and reference of measurement traceability Measurement system organization work. As of February 2020, the JCTLM database has recommended 201 reference measurement procedures for 80 projects, 303 reference materials for 173 projects, and 135 reference measurement services for 40 projects provided by 19 reference measurement laboratories [6]. In the past 10 years, the development of my country's reference measurement laboratories has made significant progress, and 8 units have entered the JCTLM reference measurement service list, accounting for about 50%. The research on reference measurement procedures and reference materials is relatively lagging behind. There are only more than 10 items on the list. There are three main reasons that restrict development. (1) At present, the reference measurement laboratory uses the reference measurement procedure documents recommended in the JCTLM database to establish measurement methods, participates in inter-laboratory comparisons of international reference measurement laboratories (such as the reference laboratory external quality evaluation plan), and establishes a management system in accordance with the requirements of ISO 15195 And passed the accreditation (such as China National Accreditation Committee for Conformity Assessment). However, optimizing or developing a new reference measurement procedure requires the establishment of a complete solution, including the use of precise measurement equipment and technology, meeting the requirements of ISO 15193, uncertainty better than conventional test results, well-trained measurement personnel, and International peer review, etc., which puts forward higher requirements for reference measurement program research. (2) The matrix that links the reference measurement system and the reference materials and calibrators for routine testing is crucial. Due to the complexity of the human sample matrix for routine testing, the measurement of the measured object is often affected by multiple factors. These complex The matrix effect caused by environmental conditions will lead to deviations in direct measurement results. Therefore, in addition to the requirements of ISO 15194, reference materials and calibrators need to evaluate their interoperability between different measurement procedures. It is also a research hotspot. To this end, the American Association for Clinical Laboratory Standards issued the EP30-A[7] and EP14-A3[8] guidelines, and in 2018 the International Federation of Clinical Chemistry and Laboratory Medicine Interoperability Working Group published an interoperability update plan[9-10] to guide and standardize interoperability evaluation. (3) The uncertainty of the measurement results represents the reference measurement capability of the reference measurement laboratory, despite ISO/IEC Guide 98-3: 2008 "Measurement Uncertainty Part 3: Guidelines for the Expression of Measurement Uncertainty" [11] General requirements, guidance from documents such as "Quantification of Measurement Uncertainty" [12] issued by the European Center for Analytical Chemistry and the International Traceability Cooperation Organization for Analytical Chemistry, and "Propagation of Monte Carlo Method Distributions" [13] issued by the International Joint Committee on Metrology, but the method performance indicators, equipment and reference materials used for running the reference measurement program in each reference measurement laboratory are different, and the introduced type A uncertainty and type B uncertainty are also different. The uncertainty of unified specifications Degree evaluation is also one of the difficulties in the research of reference measurement systems.

The article "Current Status of Standardization of Clinical Chemistry Testing" in this topic provides a more comprehensive explanation of standardization based on reference measurement procedures for laboratory medicine, consistent methods based on agreed protocols, and mutual recognition of test results; "Reference Material Interoperability Evaluation Plan" "Development of Candidate Secondary Standard Materials for Catalytic Activity Concentration of Frozen Human Serum α-Amylase" and "Uncertainty Assessment of Serum Creatinine Concentration Determination by Isotope Dilution Mass Spectrometry" 3 articles, focusing on the above hot and difficult issues, with examples Analyzed.

2 REFERENCE MEASUREMENT SYSTEM APPLICATIONS

2.1 Application in IVD Enterprises

Whether it is ISO 17511 released in 2003 or the new version of ISO 17511 released in 2020; whether it is ISO 15193 or ISO 15194, one of the keywords is IVD. In the value traceability chain, the role of IVD in connecting the previous and the next is crucial and irreplaceable. IVD transmits the value of the reference measurement program to the conventional testing system through a series of calibration schemes, and the conventional testing results are traced to the reference measurement system through IVD, thereby enabling different laboratories, at different times and different locations, to adopt The test results of different IVDs are equivalent. The article "Application and Thoughts of Medical Reference Systems in IVD Enterprises in my country" in this topic explains the basic situation and classification of reference measurement systems from the perspective of IVD enterprises, from the three aspects of reference measurement procedures, reference materials, and harmonization research The application of reference measurement procedures in IVD enterprises in my country was introduced, and the current reference measurement procedures and the number of reference materials could not meet actual needs, the IVD industry's understanding of value traceability and standardization was not perfect, and the laboratory network that could provide reference measurement services was

introduced. Problems in three aspects including lack of IVD are analyzed to improve IVD companies' understanding of value traceability and standardization, and to continuously promote the development of my country's IVD reference system.

2.2 Application in External Quality Assessment (EQA)

EQA is defined in ISO/IEC 17043:2010 [14] as the use of inter-laboratory comparisons to evaluate participants' abilities according to pre-established criteria. Determining the target value is one of the keys to the EQA plan. The most commonly used method is to use the method of consensus value among participants; if commercial quality control materials are used, the impact of matrix effects needs to be considered and the method of group evaluation of the detection system must be adopted. In recent years, with the development of reference measurement systems, EQA providers have begun to use reference measurement procedures to assign values to human samples, that is, using the reference value as the target value to directly compare the results of each participant. The reference value can be traced to National standards or international standards, namely the truthness verification program (TVP). Among my country's EQA providers, the Clinical Laboratory Center of the National Health Commission and the Shanghai Clinical Laboratory Center have carried out various TVPs. Participants understand the correctness of laboratory test results by participating in TVP and continue to improve; providers use unified target values to evaluate the testing capabilities of all participants and promote mutual recognition of results. The article "Application value of apo A1 and apo B candidate reference methods in room quality assessment" in this topic introduces the establishment of the reference measurement procedure and its application in EQA. The application of reference measurement procedures in EQA provides technical support for mutual recognition of inspection results.

3 SUMMARY

The purpose of laboratory medicine is to ensure that the measurement of laboratory medical quantities can be applied correctly in medicine and be comparable no matter when and where. Quantities need to be clearly defined and reported results must be accurate (correct and precise). Conducting research based on reference measurement systems will ensure the accuracy of measurement results from the source and the equivalence of routine test results in various clinical laboratories. It is believed that with the joint efforts of domestic and international regulatory agencies, IVD companies and clinical laboratories, my country's reference measurement system will continue to develop and continue to meet the needs of clinical diagnosis and treatment.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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