Guidance for approving clinical molecular pathology tests.

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Abstract

Identity testing, cancer screening, human leukocyte antigen typing, pharmacogenetics, and other fields continue to see an increase in the usage of DNA- and RNA-based diagnostics. The enormous increase in information about the molecular causes of disease and the development of technological capabilities are two factors that contribute to progress. Every molecular test may have limits that need to be carefully evaluated before being used in clinical settings in addition to the requirements for clinical utility. Through the process of test validation, analytic and clinical performance features, as well as test limitations, are identified and recorded. To give a reasoned method for integrating molecular testing into the clinical laboratory, it is necessary to outline the accepted principles of test validation and pertinent laws in the United States.

Keywords: Clinical Laboratory Standards Institute, Hematopathology, Test validation.

Introduction

Although it is crucial to learn pertinent vocabulary in order to comprehend the concepts of test validation, the governing organisations typically do not make an effort to explain these terms. As a result, there may be significant differences in how these phrases are understood by different laboratories and organisations. The Clinical Laboratory Standards Institute (CLSI) makes an effort to define terms used in its texts precisely. Because separate consensus groups drafted the CLSI publications at various times and the meanings had evolved and changed, the documents do, nonetheless, contain some contradictions. To "promote wider acceptance and utilisation of internationally approved terminology," the CLSI now offers a "Harmonized Terminology Database" that is open to all users. Clinical validity focuses on the linked diseases or patient conditions, whereas analytical validity concentrates on the analyte(s) targeted by the assay. Finding and evaluating potential sources of technical variation in the analysis of patient samples is one of the objectives of analytical validation [1].

According to the test, different performance characteristics must be addressed during the analytic validation process due to different technological variation sources. Molecular testing has historically been mostly qualitative, having its roots mostly in hematopathology and genetic testing; but, with improved technology and applications, quantitative molecular testing has become widespread. In terms of both their performance characteristics and their design, quantitative molecular tests that assess factors like gene dosage, tumour burden, or viral load are considerably more similar to conventional chemical tests. Finding and measuring potential causes of biologic variation in the analysis of a given sample is one of clinical validation's main objectives. The degree to which the test is beneficial medically is influenced by this procedure. A specific test offers useful data that can help guide the management of a patient by establishing the "normal" and "abnormal" ranges of values [2].

It is important to maintain the separation between analytical and clinical performance traits. Consider, for instance, that while an allele-specific polymerase chain reaction may reliably identify a specific CFTR gene mutation, it only does so for one of the over 1000 known disease-causing mutations. Even while the positive agreement to the comparative test is good for detecting the single mutation, its clinical sensitivity for cystic fibrosis diagnosis would be low.

Strategy for test validation

Phase of Planning to Establish Test Requirements: Finding the test's intended purpose is the first stage, and using this knowledge, choosing the best test design and the test's anticipated performance characteristics is the following. Even though sometimes ignored, this stage is crucial to creating the validation plan.

Produce Validation Data*:* Writing the validation strategy, producing the data, and compiling the data into a validation summary report constitute the second stage. A number of guidelines for creating and implementing test validation methods have been issued by CLSI.

Conduct the Test*:* The test must be incorporated into the laboratory's process, and paperwork must be finished. An implementation checklist is quite helpful because of the amount of information needed. The laboratory director

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must write and sign a thorough procedure that includes all necessary information, including indications, intended use, test principles, how to handle and store samples, reagents, controls, equipment, step-by-step instructions, and references. Worksheets for testing and reporting purposes could be included in other papers [3].

There must be a process for quality control and quality assurance before a test is implemented. Pre analytic, Analytic, and Post analytic concerns, many of which may be General, but some of which may be Particular to the Test System, should be addressed in this approach. Important quality control and quality assurance indicators including cycle times, documentation of control failures or test failures, trends in test volumes and outcomes, and others should be incorporated into this approach. The percent of positive outcomes should be fairly stable; for instance, if the patient population is kept constant throughout time and the number of patients with factor V Leiden positivity is tracked. An examination would be prompted by a large shift in volume or promising outcomes. One step in the standards and quality assurance process for quantitative or semi quantitative tests are designing the calibration scheme [4].

According to CLSI, a calibrator is a substance, material, or product designed by its manufacturer to be used to establish the measuring relationships of a medical device for in vitro diagnostics. Reference material is a term that refers to a substance whose properties are sufficiently homogeneous and well-established to be used for the calibration of an apparatus, the evaluation of a measurement method, or for putting a value on materials. CLSI adds the note that a specific reference material may be used either as a calibration material to synchronise a measurement system and put a value on materials, or as a test substance to determine whether a measurement method is accurate. Alternatively, it can be used as a control material to evaluate how well a measurement process worked, although it cannot be used for both purposes simultaneously in the same laboratory. This is so that the controls can be used to evaluate the test system as a whole, whilst the calibrators are deemed to be a part of the test system. Thus, a control that is separate from the test system may be utilised both as a control and to confirm calibration. In a matrix appropriate for the clinical specimens evaluated, calibrators and materials for calibration verification should ideally be located. A minimum of every six months, as well as during service interruptions or reagent lot changes, calibration verification must be carried out [5].

Conclusion

The application of evidence-based laboratory medicine requires test validation. Before a test is used in a clinical laboratory, it needs to be effectively verified or validated. It is reassuring to know that a laboratory's efforts reassure patients and the public that we in the health care system are operating in their best interests, even though the task might at times feel daunting. The work that lab professionals do to increase accessibility and promote laboratory medicine should be celebrated.

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