

FDA-approved, Nonwaived Laboratory Tests: Method Validation, Performance Standards, and Biological Variations

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LEARNING OBJECTIVES

1. Compare and contrast waived and nonwaived tests.
2. Differentiate test evaluation from test validation and explain the steps included in these processes.
3. Identify the main components of a test procedure.

ABSTRACT

Laboratory Medicine is described as the use of clinical laboratory tests to make diagnostic decisions. Laboratory tests are used to diagnose or confirm a specific condition or disease, monitor a patient's condition or response to treatment, and to aid in the early detection and determine the prognosis of disease. During the earliest years of laboratory medicine, clinical pathologists manually performed, interpreted, and communicated test results to physicians. However, the continuous advancement of medicine has demanded advanced methodologies and laboratory testing to be researched, developed, clinically evaluated, and ultimately performed by laboratory professionals. This article describes the process and guidelines for implementing new laboratory tests into clinical laboratories.

ABBREVIATIONS: CLIA - The Clinical Laboratory Improvement Amendments, FDA - Food and Drug Administration, r - correlation coefficient, QC - quality control, RE - random error.

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INDEX TERMS: test implementation, method validation, analytical measurement range, biological variation, individualized quality control plan.

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INTRODUCTION

In the United States of America, laboratories must be licensed by the department of health to process patient samples. The federal government established a federal code of conduct to manage and monitor clinical laboratories. The Clinical Laboratory Improvement Amendments (CLIA) are a group of rules that were established in 1988 to help regulate clinical laboratories, provide guidelines to the scope of testing, and protect consumer rights. CLIA divides laboratory testing into waived and non-waived tests based on the complexity of the analysis (Figure 1).

Waived tests require minimal technical competency and they yield low risk in the event of an erroneous result. Any individual can perform a waived test in a physician office or their home and no educational or professional training is required. If the test is performed in a physician's office, the office must apply for a CLIA certificate and the facility that performs the test must comply with all the manufacturer recommendations. CLIA doesn't demand any other regulations for waived tests.

Non-waived tests are defined as either moderate or high complexity. Unique educational and professional experience are required to perform non-waived tests. CLIA and the Food and Drug Administration (FDA) determine the complexity of the test, using specific criteria.¹ Health care facilities that perform non-waived tests must obtain a CLIA certificate and abide by CLIA regulations. In addition, the facility must be inspected periodically and provide proof that they comply with the CLIA quality requirements. All laboratory developed tests and non-FDA approved tests are classified as high complexity tests, and CLIA requirements are more rigorous for these kinds of tests.¹

Laboratory assays are developed based on the need to test for a specific substance, to monitor a particular process, or for a faster and more accurate methodology.² In the past few years, clinical research determined that Vitamin D deficiency contributed to many diseases and conditions. The discernment led to the need for an assay to monitor Vitamin D levels. Likewise, the need to improve the

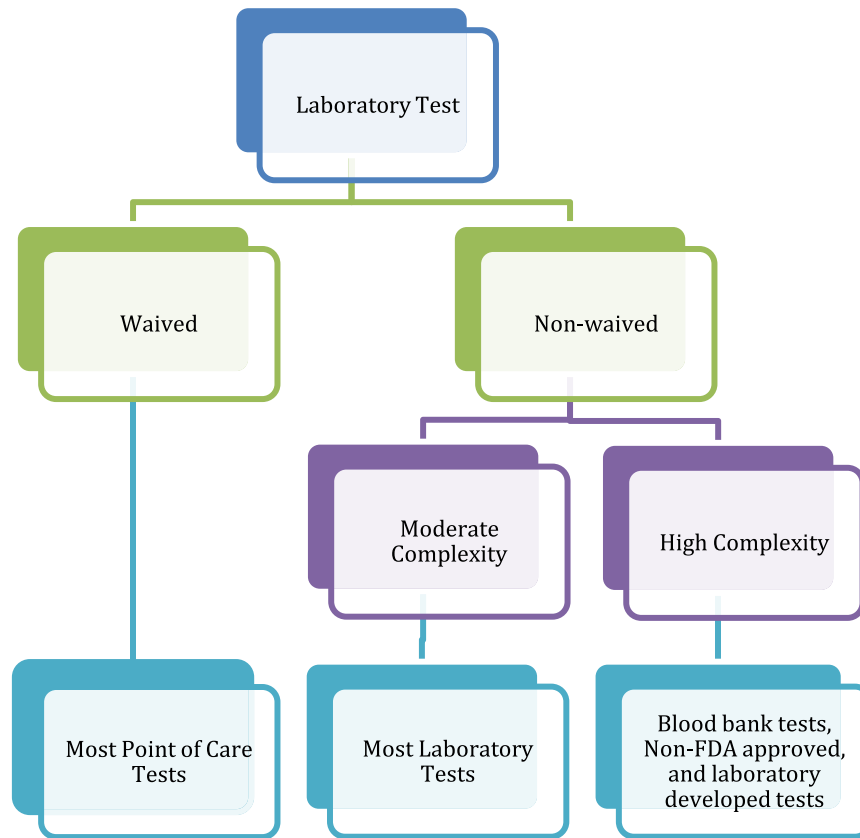


Figure 1. Test complexity determined by CLIA and the FDA.

turnaround time for microbial culturing methods contributed to the development of Polymerase Chain Reaction techniques that determine the presence or absence of specific microorganisms in patient specimens. Polymerase Chain Reaction techniques can identify microorganisms within two hours with high accuracy, while cultures require 48 to 72 hours.

Development and Implementation of a Clinical Laboratory Test

Before a new laboratory test is available for implementation in clinical settings, it must go through the following phases: 1) research and development to prove usability, 2) clinical evaluation to determine the test sensitivity and specificity, 3) manufacturing, in which the manufacturer determines the capability to reproduce the test assay in mass quantity, and 4) review by regulatory organizations in which the test complexity is classified. The test is then cleared to be used by health care professionals.³

Once the need is determined for implementing a new test, laboratory professionals must assess the analytical and clinical performance of the assay and verify that the test performance matches the manufacturer specifications. Additionally, validation on the new laboratory test must be performed to prove that it fulfills its intended use.

Regulatory organizations require that clinical laboratories follow CLIA requirements, including the following evaluations, for non-waived tests.⁴

METHOD VALIDATION

The details of a method validation are described in this focus series in, "Eight Steps to Method Validation in a Clinical Diagnostic Laboratory." Briefly, precision, accuracy, and linearity, as described below, are considered part of the method validation process. To adopt a new clinical laboratory test, it is important to determine what values for precision and accuracy are acceptable. Total error, random error (RE), and systematic error should be calculated for the new test and compared to the total allowable error range published by CLIA. Furthermore, as detailed in "Performance Standards for Quality Control Systems," the quality of an assay must be monitored by quality control (QC). Setting and using quality goals allows laboratories to design an efficient QC system and select error detection limits specific to the quality level of each analyte. Generally, the error for any of these values must be less than or equal to the CLIA requirements and follow the acceptable published biological variation data for the measured analyte.⁵

Accuracy

Accuracy is the process of comparing a measured value to the target (true) value. In a clinical laboratory, accuracy of a new method is determined by comparing the results from the new method to the method in current use (a gold standard). Samples that cover that entire reportable range are tested by both new and old methods concurrently. Laboratory professionals may use statistical analysis software to evaluate the accuracy of such an experiment and calculate the correlation coefficient (r).⁶ r indicates the linear relationship between the two methods. The ideal value for r is +1 or -1. If $r < 0.975$, it indicates a weaker linear relationship. RE influences the value of r .⁶

Precision

Precision is the closeness of one measurement to another. Precision may be determined by running QC samples 20 times over 20 days by different personnel at different times of the day. The results can be used to calculate the mean, SD, and coefficient of variation. A low coefficient of variation indicates better precision and a lower chance of RE.⁶

Linearity (Reportable Range Verification)

The analytical measurement range is the range of results that the test can produce without performing any dilutions. Linearity is determined by running samples with different analyte concentrations that cover the entire reportable range of the method. The determination includes samples that are at and within the predetermined reportable range and at the extreme low and high ends of the reportable range. The results are usually plotted on a graph, and the range of the results should match the true sample concentrations.⁶ A straight line indicates that the system is linear throughout its reportable range.

Biological Variation

Patient test results are used to reflect the patient condition. A large change in the results may indicate a new patient condition or poor sample quality. Data regarding biological variation can be used to determine if the change in two consecutive test results is significant. The laboratory can set the laboratory information system to alert the user when a highly significant change occurs (delta check).⁷ In this focus series, the role of biological variability in implementing a new assay into a clinical laboratory is described in greater detail in "The Generation and Applications of Biological Variation Data in Laboratory Medicine."

CONCLUSION

The process of implementing a new laboratory test, while time consuming, is a crucial one. A well-executed validation study results in good outcomes. Rushing through the process can impact the quality of the test results which, as a result, can impact patient care.

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