Metrological Traceability of Assays and Comparability of Patient Test Results

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KEYWORDS

• Metrology • Traceability • Standardization • Harmonization • Comparability

KEY POINTS

- As of 2003, metrological traceability of assay calibrators has been a regulatory requirement and necessary to ensure accuracy and comparability of patient test results.
- Calibrator traceability and comparability of test results from different assays are necessary for the use of electronic health records and optimal patient care.
- Calibrator traceability is one significant aspect of the standardization of clinical laboratory practice, which includes standardization of other facets, including reporting units, test nomenclature, and evidence-based laboratory medicine guidelines.

INTRODUCTION

The clinical laboratory field is experiencing globalization. Laboratory practice is moving toward harmonization and the ability to produce comparable patient test results. Greenberg observed, "An increasingly important objective in laboratory medicine is ensuring the equivalency of test results among different measurement procedures, different laboratories and health care systems, over time."[1,2] Metrological traceability is required to provide equivalence of results from diverse analytical systems.[3] Laboratories no longer work in isolation, and harmonization of laboratory testing is far-reaching, including all aspects of the total testing process (TTP).[4] The goal is "Right result, Right patient, Right time, Right form, Right test choice, Right interpretation, and Right advice." Test results must be equivalent to use universal clinical guidelines for disease diagnosis and patient management. Impediments to harmonization include inadequate measurand (analyte) definition, lack of analytical specificity, noncommutability of reference materials, lot-to-lot variability of reference materials and

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assay reagents, and a lack of systematic approaches to standardization. These issues affect patient care because physicians fail to understand the limitations of laboratory measurements, including the lack of interchangeability of results from different analytical methods.[5]

Generating comparable results remains a holy grail due to use of multiple assays for the same analyte, potentially causing different clinical interpretations.[5,6] Clinical decision values (cutpoints) are decided by international expert groups without consideration of analytical disparity. Even advances in technology are not always an improvement. As noted by White, "frustration at the lack of significant progress…was captured in the title 'Accuracy in Clinical Chemistry — Does anybody care?', in which Tietz identified that the accuracy of many routine laboratory methods had declined as use of faster, automated methods and instrumentation increased. Since Tietz's *cri de coeur*, there has been significant progress with both the theory and the practice of implementing a coherent reference system for measurements in clinical laboratories."[6] Harmonization was not possible historically due to a lack of established reference materials and methods. Miller and Myers[7] noted, "True and precise routine measurements of quantities of clinical interest are essential if results are to be optimally interpreted for patient care. Additionally, results produced by different measurement procedures for the same measureand must be comparable if common diagnostic decision values and clinical research values are to be broadly applied."

A patient's test history would be consistent if only one laboratory performed all testing (same methodology, analyzer, and so forth), so a significant change in concentration would signal a meaningful clinical change. But patients are increasingly mobile and multiple laboratories may test their samples so results may not be consistently interpreted.[8] Harmonization can produce essentially equivalent results (not quantitatively equal but clinically equivalent) and changes in concentration can be correctly interpreted.[9] Harmonization needs to include nomenclature, units of measurement, and other factors for use of evidence-based clinical practice guidelines.[8,10] Physicians expect results to be interchangeable even though analytes can be measured by multiple methods. Many clinicians do not realize tests performed by one method cannot be reliably compared with those from another method. This lack of comparability creates barriers to sharing laboratory results across health care systems and can have adverse patient consequences.[11] For some analytes, reference materials do not exist or there is a limited supply, and new lots may not be identical to the original material.[10] It is even difficult to know which molecule is actually being measured given structural variability, for example, the various forms of human chorionic gonadotropin (HCG).

Lack of harmonization has real adverse clinical consequences, and prostate-specific antigen (PSA) is a prime example.[6,12–14] An early PSA assay (Hybritech, San Diego, CA) used the manufacturer's calibrator, and the standard 4.0 mg/L PSA cutoff for prostate cancer was established. Other assays use calibrators traceable to World Health Organization (WHO) international reference material (WHO 96/670 and 96/668). A 2004 study of 2304 patients compared PSA results from assays using the Hybritech or the WHO calibrator. Of 288 patients, 55 (19%) exceeded the PSA 4.0-mg/L cutoff based on the Hybritech calibrator result but were not candidates for prostate biopsy by the WHO-calibrated results. In another PSA study, 106 men were tested using both the Hybritech and WHO traceable calibrators and WHO calibrator results were 20% lower. Depending on the assay, some men are candidates for prostate biopsy (a definitely invasive procedure) and others are not. Many clinicians are unaware, however, that different PSA results are produced for the same patient sample if tested by assays using different calibrators, resulting in different clinical interpretation and adverse patient consequences. Lack of comparability is a concern for immunoassays,