

# The Need to Harmonize Clinical Laboratory Test Results

A White Paper of the American Association for Clinical Chemistry

July 2015



# Table of Contents

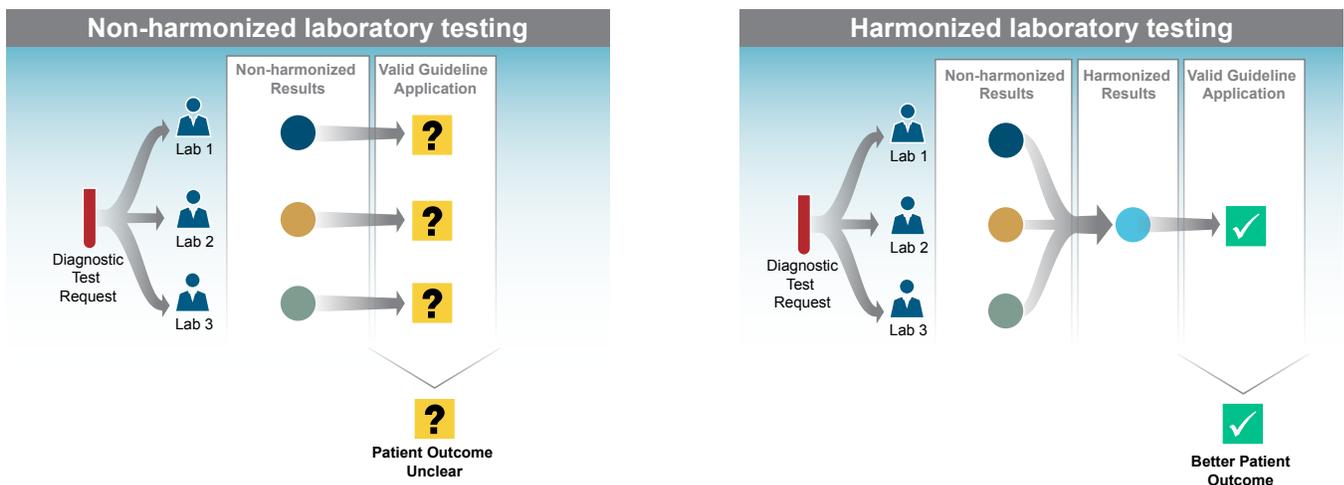
Executive Summary.....	iii
The Problem: Some Lab Tests Lack a Gold Standard, and Results Vary from Lab to Lab .....	iii
How Patients and Providers Are Affected .....	iii
What Laboratory Experts Are Doing .....	iv
Background.....	iv
Benefits of Clinical Laboratory Test Harmonization .....	iv
Barriers to Harmonization .....	v
Recommendations.....	v
Conclusion .....	v
I. Background.....	1
What Are Clinical Laboratory Tests? .....	1
Clinical Laboratory Test Procedures .....	1
Role of Clinical Laboratory Testing in Healthcare .....	1
The Need: Accurate and Comparable Clinical Laboratory Test Results .....	2
Purpose of this Report.....	3
II. Importance of Clinical Laboratory Test Harmonization .....	5
Clinical Guidelines .....	5
High-Quality Healthcare.....	6
Medical Errors .....	7
Healthcare Costs .....	7
III. Barriers to Harmonization .....	9
Lack of Appropriate Reference Measurement Procedures or Certified Reference Materials .....	9
Inadequate Definition of and Specificity for Tested Substances (Analytes).....	10
Lack of Universally Accepted Protocols and Oversight for Harmonization .....	10
Inadequate Funding and Other Resources .....	10
IV. Case Studies .....	11
Case Study of a Non-Harmonized Test: Prostate Specific Antigen (PSA) .....	11
Case Study of a Harmonized Test: Hemoglobin A1c Test for Diabetes .....	12
V. Recommendations.....	13
VI. Conclusion .....	14
References .....	15
Glossary.....	18
For More Information .....	20

## Executive Summary

### The Problem: Some Lab Tests Lack a Gold Standard, and Results Vary from Lab to Lab

When a patient enters an emergency room, visits the doctor's office, or spends time in a hospital, nurses and doctors almost invariably depend on lab tests to provide patient care. Whether it is an emergency like a heart attack, an infectious disease such as HIV, or cancer, accurate laboratory tests give healthcare professionals vital insights so patients get the care they need.

While most laboratory tests are very reliable, there is not yet a gold standard that clinical laboratory experts and scientists agree upon for many tests. Unfortunately, this means that a test result at one hospital may yield a significantly different answer compared to another hospital or reference lab — even in the same city. Experts call this a lack of harmonization. A test that is harmonized provides the same results regardless of the manufacturer or lab.



### How Patients and Providers Are Affected

When laboratory tests are not harmonized, the entire continuum of patient care can be affected in profound — but not always obvious — ways. For example, as medicine moves toward evidence-based guidelines as a way to ensure the best care for the population, often these guidelines are anchored in lab test results. However, if the test used in a guideline is not harmonized, test results do not always align with the guideline, which can mislead physicians and defeat the purpose of following the guideline. Other critical benefits of harmonized tests include:

- **Fewer medical errors:** Harmonized laboratory tests allow more accurate decision making by physicians, reducing diagnostic and treatment errors that result from too much variation in test results.
- **Lower healthcare costs:** False-positive or false-negative results from non-harmonized clinical laboratory tests can lead to unnecessary follow-up diagnostic procedures and treatments, adding unnecessary costs to patient care.

## What Laboratory Experts Are Doing

Successful harmonization efforts have already been completed for some critical tests, such as cholesterol for heart disease and hemoglobin A1c for diabetes. These efforts have already reaped benefits in improved outcomes and lower costs. AACC recommends that laboratory professional organizations partner with the Centers for Disease Control and Prevention and other public health stakeholders on similar efforts to harmonize additional important tests.

## Background

Clinical laboratory tests are medical procedures to test specimens of blood, urine, or other tissues or substances from a patient. Examples include tests to measure levels of cholesterol in blood and protein in urine. Healthcare professionals use clinical laboratory test results to diagnose diseases, plan treatments, assess responses to treatment, and monitor patient health.

Clinical laboratory tests are essential for providing high-quality healthcare, but test results can be misinterpreted unless steps are taken to ensure the results are consistent, regardless of where or when they are performed. Harmonization, a process to ensure that different clinical testing procedures used by different laboratories give equivalent results, is a concept that can be applied to foster greater consistency. Harmonizing test results will enable healthcare providers to use clinical guidelines with greater confidence for diagnosing disease and managing patients. Congress recognizes the importance of harmonization and supports a public-private partnership to address this issue.

## Benefits of Clinical Laboratory Test Harmonization

Several critical aspects of healthcare would benefit from harmonized clinical laboratory tests:

- **Improved clinical guidelines:** When clinical practice guidelines that inform diagnosis and treatment are based on specific values for laboratory test results, the broad success of those guidelines depends on harmonized test results. Significant differences in values from lab to lab or over time limit the applicability of guidelines.
- **Better-quality healthcare:** Harmonized clinical laboratory tests help ensure reliable screening and diagnosis so that appropriate treatments are provided. Physicians can be confident in their diagnosis and treatment decisions only if they can rely on the values reported by the lab.
- **Fewer medical errors:** Harmonized laboratory tests allow more accurate decision making by physicians, reducing diagnostic and treatment errors that result from too much variation in test results.
- **Lower healthcare costs:** False-positive or false-negative results from non-harmonized clinical laboratory tests can lead to unnecessary follow-up diagnostic procedures and treatments, adding unnecessary costs to patient care.

## Barriers to Harmonization

There are a number of barriers to the harmonization of clinical laboratory test results. Foremost is that no reference measurement procedures or certified reference materials exist for many tests. In some cases, reference materials exist but they have deficiencies that prevent them from being suitable for use as reference standards. Consequently, device manufacturers do not have reference standards to calibrate their instruments and therefore must use procedures that are not scientifically adequate because no alternative is available. The lack of urgency to address this deficiency by policymakers and the public prevents appropriate allocation of resources for the research needed to develop technically sound approaches for harmonizing laboratory test results.

## Recommendations

The active involvement of many stakeholders — including clinical practice groups, professional laboratory associations, public health organizations, national standards development groups, *in vitro* diagnostic medical device manufacturers, regulatory agencies, and payers — will be required to harmonize clinical laboratory test results. We recommend the following policy objectives for accomplishing this goal:

- Educate healthcare providers, patients, and policymakers about the variability in laboratory test results and the value of harmonizing these results
- Streamline and standardize worldwide regulatory processes to expedite the recalibration of regulated *in vitro* diagnostic medical devices with the goal of harmonizing test results based on international consensus recommendations
- Base clinical practice guidelines for interpreting laboratory test results on harmonized testing procedures
- When reference methods or appropriate reference materials are not available, harmonize clinical laboratory test results among different measurement procedures based on a consensus approach
- When reference methods or appropriate reference materials are available, harmonize all clinical laboratory test results based on calibrations that are traceable to these reference standards (also called “standardization”)
- Obtain government and private sector funding to harmonize high-priority laboratory tests

## Conclusion

Harmonized test results will ensure that clinical guidelines calling for the use of laboratory tests lead to appropriate care by enhancing the reliability of screening to detect diseases early, by producing more accurate diagnoses, and by preventing treatment errors. In addition, harmonized clinical laboratory tests will prevent unnecessary — and expensive — follow-up diagnostic procedures and treatments based on inaccurate test results.



# I. Background

## What Are Clinical Laboratory Tests?

Clinical laboratory tests are “medical procedures that involve testing specimens of blood, urine, or other tissues or substances in the body” [1]. Examples include tests to measure levels of cholesterol in blood and protein in urine. Healthcare professionals use clinical laboratory tests to screen patients without symptoms for a disease or to diagnose a disease or medical condition. Clinicians also use laboratory test results to plan treatment, assess response to treatment, and monitor patient health.

## Clinical Laboratory Test Procedures

When a healthcare practitioner orders a clinical laboratory test, a specimen is collected from the patient and sent to a laboratory. The laboratory then analyzes the specimen to measure the amount of a biological marker or other factor related to the patient’s medical condition. The laboratory sends the test results with an interpretation to the healthcare professional who ordered the test. The results and interpretation provide information on the patient’s medical condition that the healthcare practitioner uses to make a diagnosis or treatment decision. Approximately seven billion clinical laboratory tests are conducted each year in the United States [2]. Slightly more than half of these tests are performed in hospital laboratories, and the rest are done in independent laboratories, doctors’ offices, and patients’ homes.

## Role of Clinical Laboratory Testing in Healthcare

Clinical laboratory tests have many important roles for patients, healthcare providers, professional societies, healthcare systems, and the public sector.

Healthcare professionals use laboratory tests for [5]:

- Screening: Determine the presence or risk of disease in patients with no symptoms
- Prevention: Based on screening results, select early interventions to prevent disease
- Diagnosis: Detect the presence of a disease
- Disease management: Choose treatments that are safe and effective for each patient, develop strategies to manage the disease or condition, monitor response to treatment, speed up recovery, and prevent disability
- Prevent medical errors: Select treatments that benefit patients and don’t have unwanted effects, and make sure patients with a given disease are treated appropriately for that disease

Healthcare systems use clinical laboratory test data to measure the performance of healthcare professionals and institutions and to support the efficient use of healthcare resources [5].

Public-health systems also use clinical laboratory tests for many important purposes, such as to [5]:

- Detect infections and other agents that threaten the safety of patients and the public
- Protect recipients of blood transfusions from infections
- Identify the use of illicit and harmful substances to protect public safety

## The Need: Accurate and Comparable Clinical Laboratory Test Results

Patients and healthcare professionals assume that clinical laboratory tests performed by different laboratories at different times on the same type of specimen can be compared and that results can be reliably and consistently interpreted [6]. Unfortunately, these assumptions aren't always justified because some laboratory test results can be highly variable.

---

### Consolidated and Further Continuing Appropriations Act of 2015

In 2014, the Senate Labor, Health and Human Services, Education and Related Agencies Subcommittee identified the harmonization of clinical laboratory test results as a critical issue for improving patient care. Report language accompanying the draft Labor and HHS Appropriations bill urged the Centers for Disease Control and Prevention to work with the laboratory community to create uniform test results to reduce medical errors, to improve the quality of care and to empower patients [29]. In December 2014, Congress passed, and President Obama signed into law, the Consolidated and Further Continuing Appropriations Act of 2015, which reiterated congressional support for a federal-private partnership to address this vital issue [30].

---

Even small differences in laboratory test results can indicate that diseases or other health conditions are present, absent, or worsening. When laboratory tests don't give consistent results, patients who don't actually have a disease can receive unnecessary treatment, and patients with a disease might not receive appropriate treatment.

Many clinical practice guidelines contain recommendations that are based on specific laboratory test values. A reference interval is the range of results expected for healthy people. In the absence of harmonization, each laboratory performing its own test will have to generate its own reference intervals, which would apply only to that particular test in that particular laboratory. Due to changes over time in the performance of tests, results and reference intervals are not comparable across significant time periods, even in the context of a single lab. This variability severely limits the usefulness of clinical guidelines that rely on established medical decision points or a single set of reference intervals.

## Purpose of this Report

Some laboratory medicine experts and professional societies have become so concerned about the variability in clinical laboratory test results that they have advised healthcare professionals to carefully consider their use of certain tests. The current recommendation from the U.S. Preventive Services Task Force against routine prostate cancer screening with the prostate-specific antigen (PSA) test is one example that was based on both clinical laboratory test variability and physiologic variability in PSA levels for different prostate conditions [7]. Laboratory tests are so integral to many healthcare decisions that the problem of variability in laboratory test results must be addressed.

Harmonization offers a way to ensure that when different laboratories perform the same test using different measurement procedures, even at different times, the results are reliable for medical decisions and can be compared to monitor a patient's condition. A primary goal of harmonization is to enable the best use of clinical guidelines to diagnose disease and manage patients. See Figure 1 for examples of clinical laboratory test methods that have been harmonized or need harmonization.

### Figure 1: Examples of Harmonized and Non-Harmonized Clinical Laboratory Tests

---

#### Examples of harmonized tests:

- Cholesterol (cardiovascular disease)
  - Creatinine (kidney disease)
  - Glucose (diabetes)
  - Hemoglobin A1c (diabetes)
  - Sodium (kidney and endocrine diseases)
- 

#### Examples of tests needing harmonization:

- Human growth hormone (growth abnormalities)
  - Thyroid stimulating hormone (thyroid disorders)
  - Prostate-specific antigen (cancer)
  - Testosterone (cancer, endocrine disease)
  - Thyroglobulin (cancer)
- 

This report begins by exploring the reasons why patients and the healthcare system need harmonized clinical laboratory test results. The report then describes the barriers to achieving harmonization, followed by two case studies — one clinical laboratory test that needs to be harmonized and one that has achieved harmonization. Finally, the report offers recommendations for harmonizing clinical laboratory tests. A references list and glossary of technical terms are available at the end of the report. See Figure 2 on the next page for explanations of key concepts used throughout this report.

## Figure 2: Key Concepts Related to the Harmonization of Clinical Laboratory Tests

---

**Harmonization** is the process of ensuring that the results of different laboratories using different clinical laboratory tests at different times to measure the same substance are equivalent within clinically meaningful limits [8]. Clinically meaningful limits are the maximum amount of variability in laboratory test results that will not affect patient care.

---

**Calibration** is a process for establishing the relationship between the amount of the measured substance actually present in a specimen and the amount that is determined by a measurement procedure. When a clinical laboratory test is calibrated correctly (see definition of “traceability” below), it can accurately measure the target substance.

---

**Certified reference materials** are substances to be tested whose composition and amount are known [9]. A reference material may consist of a pure substance (such as powdered glucose or cholesterol) that is used to prepare calibrators for a measurement procedure. Alternatively, a reference material might consist of a well-characterized substance in a form that closely resembles the clinical specimen to be tested (e.g., blood or urine).

---

**Commutability** refers to a reference material’s ability to react in the same way as patient specimens in clinical laboratory tests. Commutable reference materials are suitable calibrators for clinical laboratory tests that are used to measure patient specimens.

---

Laboratories use **reference measurement procedures** as standards to make sure that the results of a clinical laboratory test for a given specimen are accurate. These procedures often involve the use of sophisticated techniques that accurately measure the amount of the target substance in a certified reference material and in patient specimens.

---

**Traceability** refers to the ability to link the calibration of a laboratory test result back to a reference measurement procedure a continuous chain of comparisons or to a clinical matrix reference material (when no reference measurement procedure is available) [8].

---

**Standardization** is the achievement of equivalent results by different clinical laboratory tests conducted by different laboratories using calibration that can be traced to a reference measurement procedure. The results are consistent when this calibration is repeated at different times and in different places. Harmonization encompasses standardization and also addresses those tests that can’t be calibrated by traceability to a reference measurement procedure.

---

In addition to addressing the results of clinical laboratory tests, harmonization can apply to the names of tests, how tested specimens are collected and handled, and how test results are communicated. However, this report focuses only on the harmonization of test results.

## II. Importance of Clinical Laboratory Test Harmonization

This section highlights some of the critical aspects of healthcare that would benefit from expanded harmonization of clinical laboratory tests.

### Clinical Guidelines

Professional societies, government agencies, and other groups of experts publish clinical practice guidelines to provide recommendations for healthcare professionals on prevention and treatment strategies for certain diseases and health conditions. The use of such guidelines can enhance quality of care, standardize clinical approaches to various diseases and conditions, and reduce healthcare costs.

Clinical guidelines often advise healthcare professionals on diagnostic and treatment decisions based on whether a laboratory test result is within a given range. These guidelines also offer recommendations on how to make decisions at key points along the patient care continuum. Clinical laboratory tests provide important information to support these decisions.

One review of 1,200 evidence-based clinical practice guidelines focused on the leading causes of death (e.g., heart disease, cancer, and diabetes) and the most burdensome health conditions (e.g., motor vehicle accidents, acute respiratory infection, and high blood pressure) [2]. The results showed that over one-third (37%) of these guidelines emphasize or involve laboratory testing, and many recommend the use of clinical laboratory tests at multiple points during diagnosis and treatment.

---

#### **Example of Harmonization Need: Plasma Parathyroid Hormone**

Levels of plasma parathyroid hormone (PTH), a hormone released by the parathyroid gland, are high in patients with chronic kidney disease-mineral and bone disorder. A recent study showed that five different laboratory tests of plasma PTH gave very different results for the same patients [10]. The highest result was more than four times greater than the lowest result. Because of these differences, about half the patients received inappropriate treatment based on clinical guidelines.

Chronic kidney disease-mineral and bone disorder guidelines from several professional societies and expert panels don't take into account the substantial differences in PTH results from different laboratory tests. Thus, unless health-care professionals recognize these differences, they can't use existing guidelines to reliably manage patients with the disorder.

---

Although clinical guidelines with recommendations for clinical laboratory tests are based on published evidence, this evidence often comes from studies in which a single central laboratory used a single laboratory test method. Using such guidelines without recognizing that other laboratory tests for the same substance are not harmonized with the study method can result in erroneous diagnoses and treatment decisions [11]. These errors could threaten patient safety and increase healthcare costs.

## High-Quality Healthcare

### Diagnosis, Treatment, and Monitoring

Clinical laboratory tests are important to patient care throughout the healthcare continuum. One key use of laboratory tests is to screen patients who have no symptoms of a disease or who have a high risk of developing a disease [2]. Screening tests can detect diseases at an early stage, when they might be easiest to treat successfully. The results of these laboratory tests can also be used to prevent the development of certain diseases.

Another major use of clinical laboratory tests is to diagnose disease in patients with symptoms. Laboratory tests can determine which disease a patient has, the severity of the disease, the likelihood that the patient will recover, and the patient's risk of negative outcomes.

Once the patient is diagnosed and treatment begins, the patient and his or her healthcare professional can use laboratory test results to monitor the patient's response to treatment. The clinician can also use this information to decide whether to change the treatment to improve outcomes.

Both patients and healthcare professionals use laboratory test results to make appropriate decisions about treatment. Harmonized test results would make it easier to diagnose and monitor patients and compare the risks and benefits of different treatments, including the likelihood that a patient will respond to a given treatment or that a treatment will have unacceptable side effects.

Harmonizing clinical laboratory test results would make electronic records more useful for clinicians, enabling them to compare and evaluate test results more easily over time. A patient's laboratory results may come from multiple testing facilities that use different methods, thus making it difficult to compare them. This variation in test results could contribute to medical errors and the ordering of duplicative tests.

### Patient-Centered Care

In the current environment that emphasizes patient-centered care, individuals undergoing treatment need access to their clinical laboratory test results to participate fully in their healthcare decisions. Both patients and their healthcare professionals almost always assume that laboratory tests are harmonized, even though this is often not true. As a result, correctly interpreting test results can be challenging.

Patients are often unable to obtain all of their diagnostic laboratory tests at the same clinical laboratory simply because of distance or insurance limitations [12]. If a patient has had different laboratory tests to measure the same substance or has undergone the same test at different times, differences between non-harmonized results can be easy to misinterpret.

### Provider Evaluations

Laboratory test results are used to measure the quality of care provided by health professionals and institutions [2]. Indicators of provider performance are often based in part on these providers' use of clinical laboratory tests in accordance with clinical practice guidelines as well as on the test results themselves to determine that disease management goals are met for a large percentage of patients. However, laboratory test results can only serve as accurate measures of quality of care if they are harmonized to permit appropriate interpretation.

## Medical Errors

Every year, diagnostic errors affect at least 5% of U.S. adults who receive medical care that isn't expected to require an overnight hospital stay [13]. This potential threat to the safety of patients could affect 12 million adults annually. Furthermore, the study authors believed that their estimates were conservative; that is, they concluded that the number of affected patients was likely to be higher.

Although the Institute of Medicine and others have identified many causes of errors in healthcare, the field of laboratory diagnostics has been at the forefront of quality assessment and quality assurance efforts [14]. Harmonizing laboratory test results will allow for even greater progress toward helping medical professionals make better patient care decisions. Such decisions can, in turn, reduce diagnostic errors that result from too much variation in clinical laboratory tests. Clinical laboratory test results play a role in about two-thirds of important clinical decisions about prescriptions and hospital admissions and discharges [14]; harmonized test results are critical to providing accurate patient information.

### **Example: Reducing the Misdiagnosis of Kidney Disease**

Physicians evaluate the level of creatinine in a patient's blood to assess kidney function. Variation in test results, particularly around the cutoff levels, can lead to misdiagnosis or inappropriate treatment for patients.

Prior to a voluntary 2004 standardization effort for creatinine measurement in British Columbia, results of creatinine tests varied greatly between clinical laboratories. This was especially true for results that fell within normal to near-normal ranges, in which accurate test interpretation is critical to classifying a patient's kidney function.

The impact of the British Columbia harmonization effort was far-reaching. A pilot study found that among the 107 participating laboratories, 124 different instruments from six different manufacturers were being used for testing of creatinine [15]. At baseline, the average amount of measurement error was 23.9%. After creatinine tests were harmonized, the level of variation dropped to 8.7%. The authors calculated that extending harmonization throughout the province could reduce false-positive rates of creatinine test results by 84%, thereby preventing 450,000 people from being misdiagnosed and treated for stage 3 (moderate) kidney disease.

## Healthcare Costs

A few studies have assessed the costs associated with lack of clinical laboratory test harmonization and the amount of money that harmonization can save.

### **Costs of Non-Harmonized Laboratory Testing**

In 2004, a National Institute of Standards and Technology study analyzed data on calcium test results in more than 89,000 patients [16]. Calcium tests are used to diagnose certain diseases, such as parathyroid gland disorders and some types of cancer and bone disease. Normal calcium levels ranged from 8.9 to 10.1 mg/dL in adults. Patients in this study had at least one blood calcium test result of 8.9 mg/dL or higher between 1998 and 1999.

The study found that calibration errors skewed calcium test results in a positive direction (in other words, showed that the patient's calcium level was higher than it really was) by 0.1 to 0.5 mg/dL. These calibration errors were caused by a lack of traceability to standard reference materials, variations among reagents (chemicals whose reactions are used to conduct laboratory tests) or lots of calibrator

materials, and changes in instrument readings between calibrations. Such errors would produce false-positive results for hypercalcemia (abnormally high levels of calcium) that would lead to unneeded follow-up procedures — including chest x-rays, 24-hour measures of calcium in urine, and thyroid imaging — and thus would increase healthcare costs.

The authors estimated that the cost of a result that was 0.1 mg/dL higher than the correct value ranged from \$8 to \$31 per patient undergoing the test, and the cost of a result that was 0.5 mg/dL too high was \$34 to \$89 per patient. Given that about 3.5 million patients have calcium tests each year in the United States, the potential cost of errors in these test results ranges from \$60 million to \$199 million per year.

### **Savings Associated with Laboratory Test Harmonization**

The Lipid Standardization Program (LSP) of the U.S. Centers for Disease Control and Prevention (CDC) ensures standardized laboratory test results for cholesterol and other body fats through traceability to CDC's standard reference measurement procedures [9]. The laboratories in CDC's Cholesterol Reference Method Laboratory Network (CRMLN) established CDC's reference measurement procedures for cholesterol and other body fats to help manufacturers ensure that clinical laboratory tests with their devices are accurate and reproducible [17].

A study published in 2011 evaluated the costs and savings associated with the LSP and CRMLN [18]. The authors measured reductions in numbers of deaths due to heart disease between 1980 and 2000 that could be attributed to treatment with statins (drugs that reduce cholesterol concentration in the blood) that are prescribed primarily based on a patient's cholesterol level. They based these assessments on estimates of changes in numbers of deaths due to heart disease between 1980 and 2000 that could be attributed to statin treatment and cholesterol reductions.

The two CDC programs generated savings of \$338 million to \$7.6 billion per year based on the economic value of the lives saved each year. In comparison, the total cost of the LSP and CRMLN in 2007 was \$1.7 million. Therefore, the benefits of these programs to harmonize laboratory testing results vastly exceeded their costs.



### III. Barriers to Harmonization

Some of the reasons why most clinical laboratory tests are not harmonized include lack of reference measurements or materials, inadequate specificity for measured substances, lack of harmonization protocols and oversight, and inadequate resources. These are explored in more detail here.

#### Lack of Appropriate Reference Measurement Procedures or Certified Reference Materials

Standardization to a reference measurement procedure is the best way to make sure that different laboratory tests produce equivalent results for a given patient specimen. Standardized test results can be reliably reproduced at different times and in different places because they can be traced back to the same reference measurement procedure. But reference measurement procedures aren't available for every type of test, and it's not possible to develop such procedures for many tests.

When no reference measurement procedure exists, one approach to harmonization is to use a certified reference material as a common calibrator for different clinical laboratory tests. Unfortunately, many such reference materials are non-commutable, which means their overall composition makes them give results different from those in a patient sample, making them unsuitable to serve as calibrators for clinical laboratory tests.[19]. Harmonization of different test methods requires commutable reference materials.

When a new laboratory test is developed, it typically has no accepted reference measurement procedure or reference materials. Developing such materials and methods can take years because investigators first need to understand all features of the substance being measured and the specimen (such as blood or urine) containing that substance that could affect its measurement [20]. For example, investigators need to figure out which molecule in a complex mixture has important health effects [12].

Over the past two decades, laboratory medicine experts have standardized several clinical laboratory tests using reference measurement procedures. These standardized laboratory tests include those for hemoglobin A1c and cholesterol [9, 21]. These successes have contributed to significant improvements in diabetes and heart disease care.

But despite these successes, the total number of laboratory tests for which a reference measurement procedure is available that will allow standardization remains very small (approximately 80), and most existing reference materials are not suitable to be used to calibrate routine clinical laboratory test procedures because they are too different from patient samples [22].

## Inadequate Definition of and Specificity for Tested Substances (Analytes)

Our bodies contain complex mixtures of molecules. Many molecules in these mixtures have very similar properties that make them difficult to separate in measurement methods. Despite these similarities, different molecules have very different effects in normal physiology and in disease states. The specific molecule that reflects a disease condition might not be well defined enough to develop a laboratory test method that measures only that molecule and no other closely related molecules. Different test methods have variable abilities to differentiate between similar molecules. When components other than the molecule that reflects a disease or health condition influence test results, these results might be different when different test methods are used [11].

Some analytes have different forms in people with different diseases or health conditions, and a single laboratory test might not give harmonized results for all of these forms. An example is human chorionic gonadotropin, a hormone measured to find out whether a woman is pregnant, a fetus might have birth defects, or a patient has cancer (such as ovarian or testicular cancer). This hormone has different forms in pregnant women than in those with cancer [19]. Different tests might be needed to measure each form that doctors use as a marker of health status. But the specific form measured might not be clearly understood, and a test might be used that isn't appropriate for the clinical condition under investigation.

## Lack of Universally Accepted Protocols and Oversight for Harmonization

Several organizations around the world are working to harmonize various clinical laboratory test results as well as the names of tests, units for measuring analytes, and processes for reporting test results. However, these efforts aren't coordinated, partly because these organizations in different countries have different priorities and perspectives on clinical practices [11]. Furthermore, there is no coordinating body to provide a forum for communication among laboratory professionals about harmonization priorities and best practices.

## Inadequate Funding and Other Resources

The lack of dedicated funding is a major barrier to harmonization. Funding is needed, for example, to support the operation of an international consortium to prioritize and coordinate harmonization activities, to develop standard reference materials and reference measurement procedures, to validate the suitability of potential reference materials as common calibrators for clinical laboratory tests, and to collect data on outcomes of harmonization activities.

Other resources needed to make harmonization possible include:

- Universally accepted protocols to achieve harmonization when no reference measurement procedure is available
- An organized process to manage harmonization activities in the clinical laboratory community (particularly when there is no reference measurement procedure)
- Laboratory test performance requirements that are relevant to disease management
- A systematic process to identify the highest-priority substances that need harmonized test methods
- A surveillance system to monitor the effectiveness of harmonization once it's achieved

## IV. Case Studies

This section offers two case studies. The first study, on PSA testing, shows the impact of using laboratory tests that aren't harmonized. The second example, which focuses on diabetes testing, describes a successful effort to harmonize a clinical laboratory test.

### Case Study of a Non-Harmonized Test: Prostate Specific Antigen (PSA)

Prostate cancer is the second most common cancer in men worldwide, and the number of men diagnosed with prostate cancer is expected to double by 2030 [23]. High levels of PSA, a protein produced by the prostate gland, are associated with an increased risk of prostate cancer. Tests to measure PSA levels in blood are widely used to screen men for prostate cancer. These tests can measure the amount of PSA in the blood that isn't bound to other proteins (free PSA) and the amount of free PSA plus PSA bound to other proteins (total PSA). The tests are also used to monitor patient responses to prostate cancer treatment.

About half of male Medicare beneficiaries aged 66 to 99 had PSA screening tests between 2007 and 2009 at a total cost of \$447 million for the tests and downstream procedures (biopsies, analyses by a pathologist, and hospitalizations for biopsy complications) [24].

In the past, doctors recommended a prostate biopsy in men with a PSA level higher than 4.0 ng/mL to find out whether these men had prostate cancer. Recent studies have shown that men with a PSA level lower than 4.0 ng/mL might have prostate cancer, and men with higher levels don't necessarily have prostate cancer. In 2012, the U.S. Preventive Services Task Force recommended against routine prostate cancer screening with PSA testing [7]. But several professional organizations still recommend PSA screening for some men after healthcare professionals discuss the risks and benefits of this testing with these patients.

PSA tests aren't harmonized. One study, for example, compared five commonly used PSA test methods in 596 men [25]. All of the men had undergone a prostate biopsy (removal and examination of prostate tissue), which showed that 314 of the men had prostate cancer and 282 had no evidence of prostate cancer. The different PSA clinical laboratory test methods came up with different numbers of patients whose PSA levels were above or below the cutoff level of 4.0 ng/mL because these tests weren't harmonized. For example, the tests didn't correctly identify 15 to 30% of the 314 patients with prostate cancer, and they had false-positive results for 43 to 51% of the 282 men without prostate cancer. The authors concluded that this variability in results could have a major effect on physicians' decisions about whether to order a prostate biopsy.

A second study showed the difficulty of harmonizing laboratory tests even when a standard reference material is available. This study compared results from four clinical laboratory test methods that measured PSA in a standard reference material from the World Health Organization (WHO) [26]. The WHO reference material had a lower amount of bound PSA and a higher amount of free PSA than it was supposed to. The likely explanation was that bound PSA in the reference material, which was about 8 years old when the study was done, was unstable, and some of the bound PSA in the reference material apparently became free. Consequently, the WHO reference material was not suitable for use as a calibrator.

## Case Study of a Harmonized Test: Hemoglobin A1c Test for Diabetes

About 26 million Americans have diabetes, and more than a quarter of these individuals don't know that they have the disease. A test of hemoglobin A1c in blood is used to evaluate the blood sugar level in people with diabetes, to diagnose diabetes, and to screen some people for prediabetes (a condition of moderately elevated blood sugar suggesting increased risk to develop diabetes).

The American Diabetes Association (ADA) used the results of two clinical trials — the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) — to establish hemoglobin A1c targets at 6.5% or lower to indicate that diabetes is well controlled in people undergoing diabetes treatment [27]. The ADA recommends that people with diabetes have the hemoglobin A1c test two to four times a year, depending on whether they're meeting their treatment goals. The ADA also recommends hemoglobin A1c testing to screen people for diabetes who have no symptoms but have certain risk factors (for example, being overweight or obese) and those older than 44. A hemoglobin A1c level of 5.7 to 6.4% in people who have no diabetes symptoms indicates prediabetes.

The ADA first recommended hemoglobin A1c testing in 1994 [21]. But the lack of harmonized tests at that time limited the usefulness of this testing. Materials used as calibrators didn't necessarily behave like fresh blood when they were tested using several different clinical laboratory test methods. In 1996, the National Glycohemoglobin Standardization Program (NGSP) began standardizing the results of hemoglobin A1c tests to make sure that they could be compared to those of the DCCT and UKPDS. In 2001, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a standard reference material and reference measurement procedure for hemoglobin A1c.

The NGSP network has a central primary reference laboratory that uses the same standard reference measurement procedure as the DCCT. Secondary reference laboratories in the network use commercial laboratory tests to measure hemoglobin A1c in 10 frozen specimens each month. Their results are compared to those of the central laboratory and, twice a year, to those of the IFCC reference method network. Manufacturers use this reference system to certify that the calibration of their hemoglobin A1c tests used in clinical laboratories is in agreement with the reference measurement procedure.

The NGSP has tracked progress in standardizing hemoglobin A1c testing since 1996 [21]. By 1999, 80% of laboratories were reporting results as hemoglobin A1c rather than as the less useful glycohemoglobin, but results of different test procedures were still variable. By 2004, the results from different test procedures were much less variable. By 2010, the results of all methods were within 12%, and some were within 8%, of the results of the reference laboratories.

These harmonization efforts and others around the world have greatly improved the clinical usefulness of the hemoglobin A1c test. As a result, the American Diabetes Association has recommended using HbA1c for diagnosing diabetes.



## V. Recommendations

The active involvement of many stakeholders — including clinical practice groups, laboratory practice groups, public health organizations, national standards development groups, laboratory test manufacturers, regulatory agencies, and payers — will be required to harmonize clinical laboratory test results. We recommend implementing the following actions to accomplish this goal:

- Educate healthcare providers, patients, and policymakers about the variability in laboratory test results and the value of harmonizing these results
- Streamline and standardize worldwide regulatory processes to expedite the recalibration of regulated in vitro diagnostic medical devices with the goal of harmonizing test results based on international consensus recommendations
- Base clinical practice guidelines for interpreting laboratory test results on harmonized testing procedures
- When reference methods or appropriate reference materials are not available, harmonize laboratory test results among different measurement procedures based on a consensus approach
- When reference methods or appropriate reference materials are available, standardize all test results based on calibrations that are traceable to these reference standards
- Obtain government and private sector funding to harmonize high-priority laboratory tests



## VI. Conclusion

Harmonizing a greater number of clinical laboratory tests will contribute to improved healthcare in many important ways. Harmonized test results will ensure that clinical guidelines that call for the use of laboratory tests can be appropriately implemented. Reliable screening to detect diseases early, when they are easier to treat; appropriate diagnoses of diseases; correct and consistent treatment decisions; and effective monitoring of responses to treatment will be important outcomes of more extensive harmonization of clinical laboratory test results. Furthermore, by reducing incorrect interpretations of laboratory test results, harmonization can help prevent treatment errors and unnecessary — and expensive — follow-up diagnostic procedures and treatments based on inaccurate laboratory test results.

The AACC encourages all stakeholders to recognize the critical role of clinical laboratory testing in improving health outcomes and to promote increases in resources for achieving harmonization of the highest-priority laboratory tests.



## References

1. U.S. Food and Drug Administration. Laboratory Tests. 2009. [<http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/labtest/default.htm>]
2. The Lewin Group. Laboratory Medicine: A National Status Report 2008. [[https://www.futurelabmedicine.org/pdfs/2007%20status%20report%20laboratory\\_medicine\\_-\\_a\\_national\\_status\\_report\\_from\\_the\\_lewin\\_group\\_updated\\_2008-9.pdf](https://www.futurelabmedicine.org/pdfs/2007%20status%20report%20laboratory_medicine_-_a_national_status_report_from_the_lewin_group_updated_2008-9.pdf)]
3. McEvoy C. China and India: Comparing Two Fast-Growing IVD Markets. IVD Technology, 2012. [<http://www.ivdtechnology.com/article/china-and-india-comparing-two-fast-growing-ivd-markets>]
4. The Lewin Group. The Value of Diagnostics: Innovation, Adoption and Diffusion into Healthcare. 2005. [[http://www.lewin.com/~media/Lewin/Site\\_Sections/Publications/ValueofDiagnostics.pdf](http://www.lewin.com/~media/Lewin/Site_Sections/Publications/ValueofDiagnostics.pdf)]
5. The Lewin Group. The Value of Laboratory Screening and Diagnostic Tests for Prevention and Healthcare Improvement 2009. [[http://www.chi.org/uploadedFiles/Industry\\_at\\_a\\_glance/Lewin%20Report%20on%20Dx%20Tests%20\(2009\).pdf](http://www.chi.org/uploadedFiles/Industry_at_a_glance/Lewin%20Report%20on%20Dx%20Tests%20(2009).pdf)]
6. Panteghini M. Implementation of standardization in clinical practice: not always an easy task. *Clinical Chemistry and Laboratory Medicine* 2012;50:1237-41.
7. U.S. Preventive Services Task Force. Screening for Prostate Cancer: Current Recommendation. 2012. [<http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm>]
8. Miller WG, Myers GL, Gantzer ML, Kahn SE, Schönbrunner ER, Thienpont LM, et al. Roadmap for harmonization of clinical laboratory measurement procedures. *Clinical Chemistry* 2011;57:1108-17.
9. Centers for Disease Control and Prevention. Laboratory Quality Assurance and Standardization Programs. 2014. [<http://www.cdc.gov/labstandards/index.html>]
10. Almond A, Ellis AR, Walker SW, Scottish Clinical Biochemistry Managed Diagnostic N. Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease. *Annals of Clinical Biochemistry* 2012;49:63-7.
11. Miller WG, Tate JR, Barth J, Jones GRD. Harmonization: the sample, the measurement, and the report. *Annals of Laboratory Medicine* 2014;34:1-11.
12. Plebani M. Harmonization in laboratory medicine: the complete picture. *Clin Chem Lab Med* 2013;51:741-51.

13. Singh H, Meyer AND, Thomas EJ. The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations. *BMJ Quality & Safety* 2014.
14. Plebani M. Exploring the iceberg of errors in laboratory medicine. *Clin Chim Acta* 2009;404:16-23.
15. Komenda P, Beaulieu M, Seccombe D, Levin A. Regional implementation of creatinine measurement standardization. *Journal of the American Society of Nephrology* 2008;19:164-9.
16. RTI International. Planning Report 04-1: The Impact of Calibration Error in Medical Decision Making. Gaithersburg, MD; 2004.
17. Myers GL, Kimberly MM, Waymack PP, Smith SJ, Cooper GR, Sampson EJ. A reference method laboratory network for cholesterol: a model for standardization and improvement of clinical laboratory measurements. *Clinical Chemistry* 2000;46:1762-72.
18. Hoerger TJ, Wittenborn JS, Young W. A cost-benefit analysis of lipid standardization in the United States. *Preventing Chronic Disease* 2011;8:A136.
19. Gantzer ML, Miller WG. Harmonisation of measurement procedures: how do we get it done? *The Clinical Biochemist* 2012;33:95-100.
20. Miller WG, Eckfeldt JH, Passarelli J, Rosner W, Young IS. Harmonization of test results: what are the challenges; how can we make it better? *Clinical Chemistry* 2013.
21. Little RR, Rohlfing CL, Sacks DB. Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. *Clinical Chemistry* 2011;57:205-14.
22. Miller WG, Myers GL. Commutability still matters. *Clinical Chemistry* 2013;59:1291-3.
23. World Cancer Research Fund International. Cancer Statistics: Worldwide. 2013. [[http://www.wcrf.org/cancer\\_statistics/world\\_cancer\\_statistics.php](http://www.wcrf.org/cancer_statistics/world_cancer_statistics.php)]
24. Ma X, Wang R, Long JB, Ross JS, Soulos PR, Yu JB, et al. The cost implications of prostate cancer screening in the Medicare population. *Cancer* 2014;120:96-102.
25. Stephan C, Klaas M, Muller C, Schnorr D, Loening SA, Jung K. Interchangeability of measurements of total and free prostate-specific antigen in serum with 5 frequently used assay combinations: an update. *Clinical Chemistry* 2006;52:59-64.
26. Sokoll LJ, Rosenwald S, Lyons J, Elliott DJ, Chan DW. Is the WHO 90:10 prostate-specific antigen (PSA) first international reference standard really 90% alpha1-antichymotrypsin-bound PSA and 10% free PSA? *Clinical Chemistry* 2011;57:1776-7.
27. American Diabetes Association. Standards of medical care in diabetes — 2013. *Diabetes Care* 2013;36:S11-S66.

28. Courtemanche T, Mansueto G, Hodach R, Handmaker K. Population health approach for diabetic patients with poor A1C control. *American Journal of Managed Care* 2013;19:465-72.
29. Senate Subcommittee on Labor, Health and Human Services, Education, and Related Agencies FY 2015 Departments of Labor, Health and Human Services, and Education, and Related Agencies Subcommittee Draft Report. [<http://www.appropriations.senate.gov/sites/default/files/LHHS%20Report%20w%20Chart%2007REPT.PDF>]
30. House Appropriations Committee, Consolidated and Further Continuing Appropriations Act of 2015. [<http://docs.house.gov/billsthisweek/20141208/113-HR83sa-ES-G.pdf>]



## Glossary

**Accurate:** results reflect the measured substance's actual amount

**Analyte:** chemical substance being measured

**Analytical specificity:** test's ability to measure only the target substance without being influenced by other components in a patient specimen

**Calibration:** process for establishing the relationship between the amount of the tested substance actually present in a specimen and the amount that is determined by a clinical laboratory measurement procedure

**Reference measurement procedure:** used to make sure that the results of a clinical laboratory test for a given specimen are accurate

**Clinical laboratory test:** medical procedure that involves testing specimens of blood, urine, or other tissues or substances in the body

**Clinically meaningful limits:** maximum amount of variability in laboratory test results that supports optimal patient care

**Commutability:** a reference material's ability to react in the same way as patient specimens in clinical laboratory tests

**False-positive test result:** test result that incorrectly classifies a patient as having a disease that the patient does not have

**False-negative test result:** test result that incorrectly classifies a patient as not having a disease that the patient actually has

**Harmonization:** process of ensuring that the results of different laboratories using different clinical laboratory test methods at different times for a given substance are equivalent within clinically meaningful limits

**Precise:** reproducible

**Reagent:** chemical whose reactions are used to conduct laboratory tests

**Reference material:** substance to be tested whose composition and amount is known; may consist of a pure substance (such as powdered glucose or cholesterol) that is used to prepare calibrators for a measurement procedure or might consist of a well-characterized substance in a form that closely resembles the clinical specimen to be tested (e.g., blood or urine)

**Sensitive:** able to detect a substance at low levels appropriate for the clinical use of a laboratory test

**Specific:** able to correctly detect or measure only the substance of interest and no other substances

**Standardization:** achievement of equivalent results by different tests conducted by different laboratories at different times using calibration that can be traced to a reference measurement procedure

**Traceability:** ability to link the calibration of a laboratory test result back to a reference measurement procedure through a continuous chain of comparisons, or to a clinical matrix reference material when no reference measurement procedure is available



## For More Information

For more information on the “The Need to Harmonize Clinical Laboratory Test Results,” please contact:

- Cheryl Kassed, PhD, Director, Science and Research, AACC, [ckassed@aacc.org](mailto:ckassed@aacc.org)
- Greg Miller, PhD, Chair, International Consortium for the Harmonization of Clinical Laboratory Test Results, Harmonization Oversight Group; Professor of Pathology, Virginia Commonwealth University [gmillervcu@vcu.edu](mailto:gmillervcu@vcu.edu).
- Gary Myers, PhD, Vice-President, Science and Practice Affairs, AACC, [gmyers@aacc.org](mailto:gmyers@aacc.org)
- Vince Stine, PhD, Director, Government Affairs, AACC, [vstine@aacc.org](mailto:vstine@aacc.org)