
Standardizing Hormone Measurements
National Center for Environmental Health
Division of Laboratory Sciences
U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

The Problem
Hormone testing is critically important but unreliable

Laboratory testing to measure levels of the steroid hormones testosterone and estradiol is critical to help diagnose and monitor treatment of a number of serious conditions and chronic diseases. Some of these conditions and diseases are:

- **Polycystic ovarian syndrome**
- **Androgen deficiency in men, a possible precursor to diabetes or cardiovascular disease**
- **Breast disease and breast cancer**
- **Testicular cancer**
- **Prostate cancer**
- **Erectile dysfunction**
- **Infertility**
- **Osteoporosis**
- **Hypothalamus and pituitary disorders**

Despite physicians' widespread use of hormone test results, the laboratory measurement of steroid hormones is subject to extreme variability—especially when hormones are present in low concentrations, as is usually the case for testosterone in women and children, and for estradiol in men, children and postmenopausal women.

Test variability is highly consequential because even subtle differences in hormone levels might indicate health problems. Researchers, laboratory clinicians and professional associations, such as The Endocrine Society, have for many years voiced concerns about the unreliability of hormone measurements. In fact, these concerns were so significant they prompted recommendations by organizations not to use certain hormone tests.

Test variability can affect patient care resulting in:

- **Different criteria for "normal" and "abnormal" test values among different laboratories**
- **Different clinical interpretations of test results on the same patient**
- **Misdiagnoses, delayed diagnoses, or suboptimal patient care**
- **Repeat testing when patients change doctors or are referred to specialists**
- **Repeat testing when doctors change laboratories**

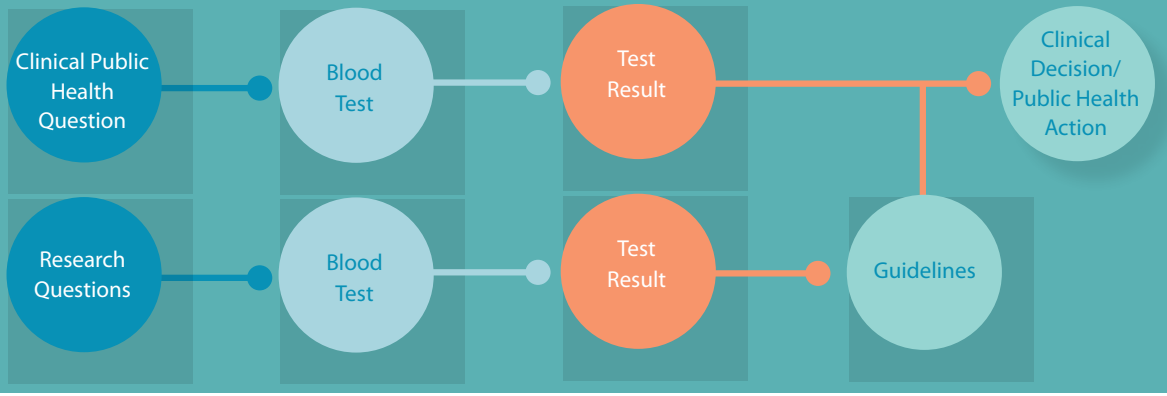
Test variability also prevents effective screening and surveying of populations in order to assess and detect public health problems. Additionally, test variability influences the outcomes of clinical trials and other research performed to improve best practice guidelines and promote evidence-based medicine and laboratory medicine practice. As of March 2010, 443 clinical trials dealing with testosterone were registered at the National Institutes of Health's clinical trials database (www.clinicaltrials.gov).

Test variability in research may result in:

- **Preventing pooling and comparing test results across studies for evidence based medical guidelines**
- **Duplicating research when new research cannot build on existing data**
- **Hampering translation of research findings into clinical practice and public health activities**

Most importantly, inaccurate test results drive up research and healthcare costs and likely cause some patients to suffer unnecessary and preventable disease complications.

Figure 1.
Meaningful clinical decisions and public health actions can only be made when tests made by researchers, physicians, and public health scientist are comparable.



The Solution
Standardized Laboratory Measurements

In 2007, CDC began a project to standardize hormone measurements to ensure accurate and comparable results across testing systems (assays), across laboratories and over time. The two key elements of the solution are the development of reference materials that have highly accurate and precise values, and reference methods that provide highly precise and accurate measurements.

Reference methods are used to assign concentrations to reference materials. Reference materials are used to calibrate assays and to verify calibrations. Thus, laboratories performing research or patient care testing can anchor their results to a common standard, regardless of the technology employed. This approach simultaneously minimizes method bias and improves method precision.

Standardized Hormone Testing Meets Many Needs

Doctors need:

- Reliable test results to make clinical decisions and monitor treatments, regardless of where or when the test is performed
- Reliable clinical guidelines and recommendations—such as cutoff values for hormones levels—to inform treatment decisions

Researchers need:

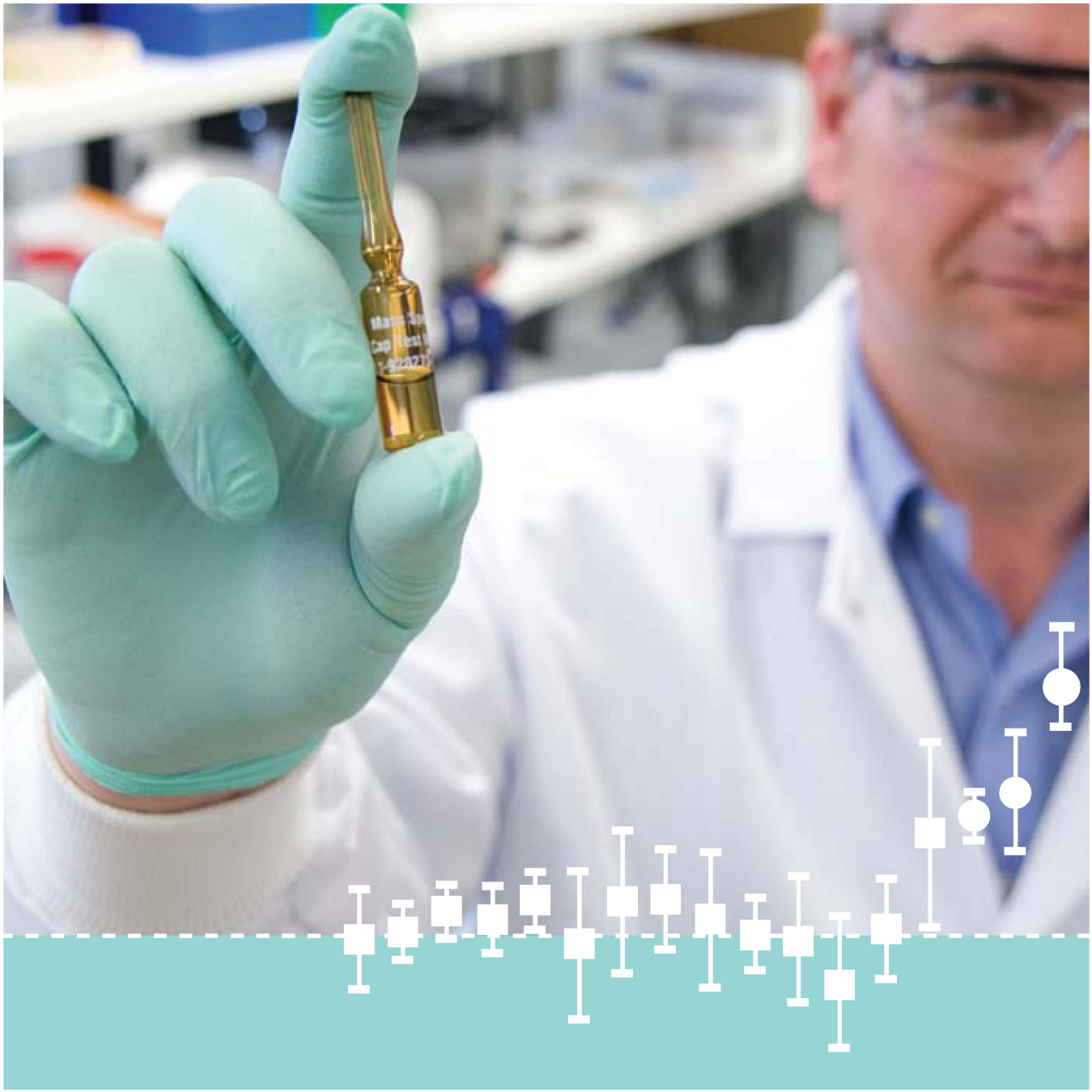
- Reliable tests to increase confidence in findings to be used as the basis for patient treatment recommendations and disease prevention efforts
- Highly sensitive and specific tests (that are able to accurately detect minute concentrations of hormones) to better determine biochemical causes of diseases and disorders

Public health scientists need:

- Reliable research findings on which to base health promotion and disease prevention interventions for the general public
- Test data that are comparable over time and across laboratories to enable accurate evaluation of public health interventions and identification of individuals at risk for disease

Health insurers and patients need:

- Measurements that are accurate and comparable across laboratories to minimize inconvenient and costly duplication of laboratory testing



CDC's Standardization Program

The four main components of CDC's Standardization Program focus on:

- Developing and implementing ***reference methods***, calibrated using "pure compound" hormones, that will be used to assign highly accurate and precise hormone values to blood serum samples. These blood serum samples will, in turn, be used as secondary reference material to calibrate specific hormone assays (Figure 3). CDC will also assess possible problems with routine assays and with other blood serum materials used to assess testing performance.

- Establishing an assay and laboratory ***calibration program*** (CDC's HoSt Project) to help assay manufacturers and certain laboratories with calibration and to assure the calibration does not change over time

- Working with the College of American Pathologists and other proficiency testing companies to develop ***laboratory surveys*** to assess and improve the measurement of testosterone and estradiol. This work will directly assess the effects of standardization on patient data.

- Collaborating with professional organizations and institutions to develop ***training and education materials*** to: a) help end-users select assays that can produce the quality data needed to reliably answer specific clinical questions; b) improve the entire testing process from specimen collection and processing to clinical interpretation of results; and c) document appropriate reference ranges of testosterone and estradiol for different population subgroups

The full scope of CDC's Standardization Program addresses the use of hormone assays from before they leave the manufacturing plant to when they are in the hands of the end-users.

Figure 2.
Four components of CDC's Standardization Program

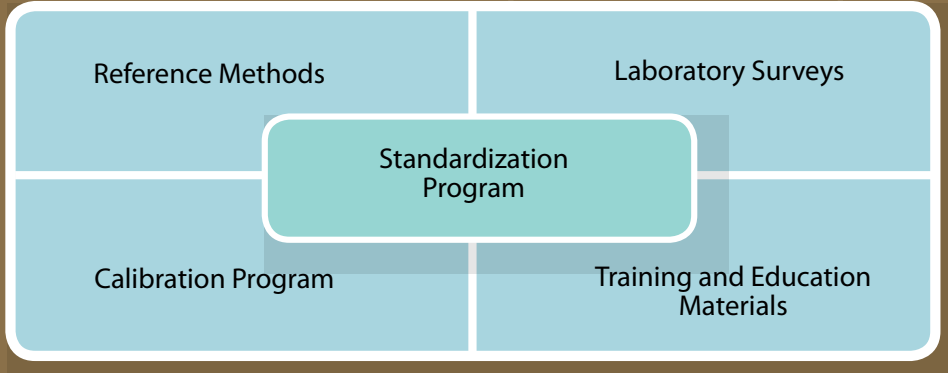
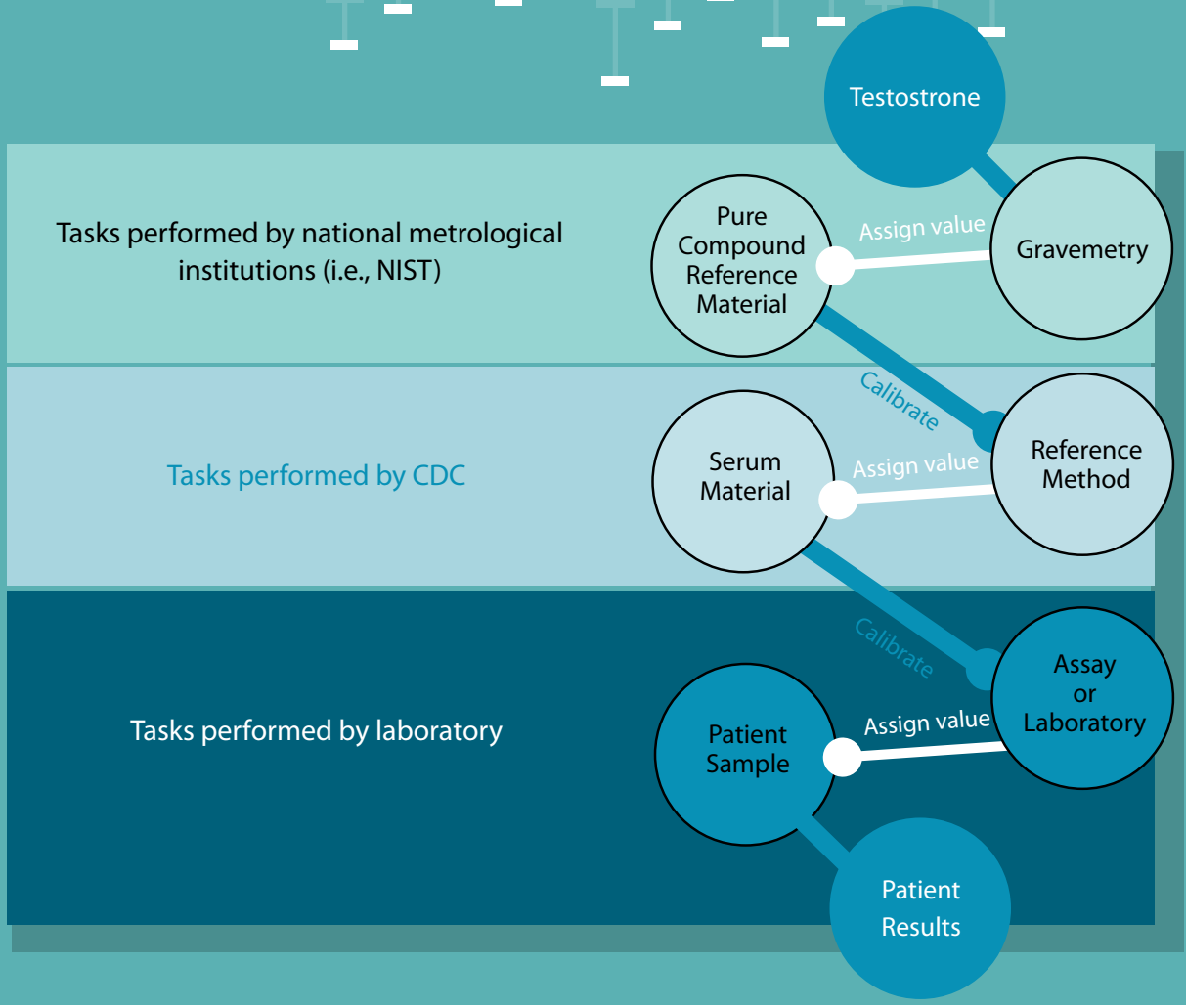


Figure 3.
Traceability provides accurate and comparable hormone measurements across testing systems (assays), across laboratories and over time. The simplified traceability chain includes roles of National Institute of Standards and Technology (NIST), CDC and laboratories.

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CDC's Hormone Standardization Project (HoSt)

The objective of CDC's HoSt Project is to improve diagnosis, treatment and prevention of diseases and disorders through the standardization of testosterone measurements. Standardization of total testosterone measurements in serum will be established through method comparison and bias estimation between CDC's Reference Laboratory and the testing laboratory. Single-unit, fresh-frozen serum samples will be used, and the observed bias will be compared to predefined limits. CDC considers a laboratory standardized when the observed bias is within the predefined limits. Participation will remain anonymous and, with the participant's approval, standardized laboratories will be listed on CDC's website by name only. CDC's HoSt Project can provide technical assistance for resolving any problems in meeting performance standards, thus ensuring the participant's long-term success in maintaining standardized testosterone measurements.

Hormone standardization builds on previous CDC work

CDC is an internationally-recognized leader in test standardization, with more than 50 years of experience in this area.

Past projects include work to characterize reference materials and standardize measurements of:

- Bone resorption markers ***pyridinoline and deoxypyridoline***, which constitute a powerful tool for investigating bone development and monitoring osteoporosis treatments
- ***Glycated hemoglobin A1c***, an important measure of plasma glucose (blood sugar) in people with diabetes and at risk for developing diabetes
- ***Total cholesterol, triglycerides and high-density lipoprotein cholesterol***, all of which are used to improve the detection, treatment and prevention of cardiovascular disease
- ***C-reactive proteins***, a general marker for inflammation and a rough proxy measure for heart disease risk

All of these programs included partnerships with other organizations to develop or improve test recommendations, guidance documents and proficiency testing programs. In addition to improving laboratory-based testing, CDC also assesses the performance of consumer products and of test systems, such as glucose monitors.

CDC's goal is to meet the urgent need in the clinical, public health and research communities for reliable data to improve patient care, promote disease prevention and conduct and translate cutting-edge studies.

Additional Information

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The Centers for Disease Control and Prevention (CDC) protects people's health and safety by preventing and controlling diseases and injuries, enhances health decisions by providing credible information on critical health issues, and promotes healthy living through strong partnerships with local, national and international organizations.

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