

CDC CLINICAL STANDARDIZATION PROGRAMS UPDATE

CDC Clinical Standardization Programs (CSP) ensure analytical accuracy and precision across measurement systems and laboratories over time. The programs provide services to laboratories, manufacturers of diagnostic products, and organizations involved in proficiency testing/external quality assessment schemes.



Spring 2022

Of Special Interest

- Thyroid Function Tests Standardization for FT4
- Cardiovascular Disease Biomarker Standardization Programs
 - Reference Materials for Apolipoproteins
 - Cholesterol Reference Method Laboratory Network (CRMLN)
 - Lipids Standardization Program (CDC LSP)
- Hormone Standardization Programs (CDC HoSt) & Vitamin D Standardization-Certification Program (CDC VDSCP)
- New Programs and Services for Biomarker Measurements
- Latest List of Newly Certified Participants for CDC HoSt, VDSCP, AMP, CRMLN and LSP

Featured Story/Highlight

Thyroid Function Tests: The new CDC standardization program for free thyroxine

Nearly 5 out of every 100 Americans ages 12 years and older have hypothyroidism [1], and about 1 out of every 100 have hyperthyroidism [2]. Every year about 12,000 men and 33,000 women are diagnosed with thyroid cancer, and about 900 men and 1,000 women die from the disease [3]. Thyroid diseases can have major, lasting effects on health if left untreated. Thyroid diseases are easily detected and effectively treated with the help of thyroid function tests. Indeed, based on data from CMS, the most frequently used laboratory tests in the U.S. are for thyroid stimulating hormone (TSH) and free thyroxine (FT4).

Clinicians and researchers have raised concerns about the accuracy and reliability of TSH and FT4 measurements for many years, which is reflected in TSH and FT4 being listed as biomarkers in need for standardization by different stakeholder groups. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established the Committee on Standardization of Thyroid Function Tests (C-STFT) to help standardize thyroid function tests by developing a reference measurement system for FT4 and a harmonization protocol for TSH. CDC's Clinical Standardization Programs (CDC CSP) are supporting these IFCC activities. The FT4 reference method has been developed and the TSH harmonization protocol is now established.

CDC CSP operates the FT4 IFCC Reference Method and assigns reference values to serum materials used in its new FT4 standardization program. As a first step, CDC CSP is conducting an interlaboratory comparison study to assess the current level of agreement among FT4 clinical assays. Compared to data from a previous study conducted by Prof. Linda Thienpont in 2016, CSP preliminary findings indicate improvements in some assays. However, high inter-assay variability still exists, and further improvement are needed. CDC CSP is collecting data and will share findings after completing data analysis. Additionally, CSP has created a panel of 40 single-donor serum samples with FT4 reference values assigned (“Phase 1” samples) that is available to assay manufacturers and laboratories. The CSP plans to launch a formal FT4 certification program by 2023.

CDC supports the C-STFT by providing technical assistance to laboratories planning to adopt the IFCC reference method for FT4. CDC is assisting C-STFT with the development of the next TSH follow-up panel to ensure continuity of TSH harmonization. In this context, C-STFT, CDC, and the National Institute for Biological Standards and Control (NIBSC), are collaborating to ensure the TSH materials from NIBSC are consistent, and to link the international units assigned to the NIBSC material with the TSH values assigned by the TSH follow-up harmonization panel.

Feel free to contact us for further information about the new CDC FT4 standardization program and related activities for thyroid function tests.

-
- [1] <https://www.niddk.nih.gov/health-information/endocrine-diseases/hypothyroidism>
 - [2] <https://www.niddk.nih.gov/health-information/endocrine-diseases/hyperthyroidism>
 - [3] <https://www.cdc.gov/cancer/thyroid/>

What’s happening at CSP

Cardiovascular Disease (CVD) Biomarker Standardization Programs

Reference Materials for Apolipoproteins

CDC CSP is the custodian and distributing laboratory for WHO/IFCC Biological Reference Materials for Apolipoprotein A-1 (Code: SP1-01), Apolipoprotein B (Code: SP3-08), and Lipoprotein(a) (Code: IFCC SRM 2B). Because the inventory of these materials will soon be depleted, CDC can only provide limited amounts per request, which should include justification on the use of these materials. CSP is working closely with the IFCC Working Group for Apolipoproteins by Mass Spectrometry (WG APO-MS) to ensure continuation of standardizing lipoproteins. As part of this work, we are developing mass spectrometry-based reference methods. These methods will be used to assign target/reference values to new reference materials.

CSP will develop programs to continue standardizing these lipoproteins. A formal standardization program will be in place once we establish the new reference measurement procedures and materials. This program will follow the same design as the CDC HoSt and CDC VDSCP programs (<https://www.cdc.gov/labstandards/>).

Updates: Lipoprotein(a) Interlaboratory Comparison Study

The IFCC Apolipoproteins by Mass Spectrometry Working Group and CSP have prioritized and are collaboratively working on Lipoprotein(a) [Lp(a)] assay standardization. The IFCC Working Group is developing a mass spectrometry-based, size-independent reference measurement procedure (RMP) for Lp(a) with traceability to an SI-based primary reference material that will be used in Lp(a) assay standardization. In preparation, CSP conducted an Lp(a) Interlaboratory Comparison Study in 2021 that included nine routine clinical laboratories as participants and covered five different assays. The objective was to determine how existing individual Lp(a) assays perform in

routine clinical settings and the degree and potential sources of variability across laboratories and assay. CSP presented the preliminary results of the study at the 2021 AACC Annual Scientific Meeting and Clinical Lab Expo. Preliminary findings show that Lp(a) sample measurements by different assays vary from 3 to 69%, with higher variances at higher concentrations. The data also suggest that the increase in Lp(a) measurement variability is not dependent on Lp(a) isoform sizes. We are compiling these data into a manuscript for publication.

Cholesterol Reference Method Laboratory Network (CRMLN)

- **Total Glycerides (TG) Certification by CRMLN:** CSP conducted the first round of TG certification for manufacturers and developers in 2021. A total of three assays are now certified for TG.
- **Isotope Dilution Mass Spectrometry (IDMS) and Abell-Kendell (AK) Method Comparison:** CDC is collaborating with the French metrological institute (LNE), the Singaporean Health Science Authority (HAS) and other partners to compare IDMS and AK methods for total cholesterol. AK methods typically reports higher values compared to IDMS. This comparison study will assess traceability and help with the accuracy of total cholesterol measurements, which improves the diagnosis of cardiovascular disease. Most of the clinical decision points are based on measurements standardized to TC AK values. There is a difference between TC AK and TC GC-ID-MS values. As mass spectrometry-based methods become more widely used, the method comparison helps ensure there is no unnoticed shift in results of assays that are standardized to mass spec-based assay.
- **Point of Care Testing:** CSP is currently reviewing the analytical performance of point-of-care testing (POCT) devices for lipid measurements. Data is being compiled and once completed, we will share findings.

CDC CSP Impact in Real-time: CSP monitors and evaluates the accuracy of CVD biomarker measurements in routine laboratories (through the **Lipid Standardization Programs-LSP**). CSP observed a negative bias trend in total cholesterol that was still within the allowable bias limit but had the potential to fall outside the limit and cause a problem in clinical use. CSP informed the manufacturer and collaborated to resolve this trend. Recent LSP data, depicted below, shows that the trend is reversing, and bias is improving. By monitoring performance in routine labs, CSP was able to address concerns before they become a problem.

Contact CDC CSP for more information on LSP and Accuracy-based Monitoring Programs (AMP) for testosterone and vitamin D.

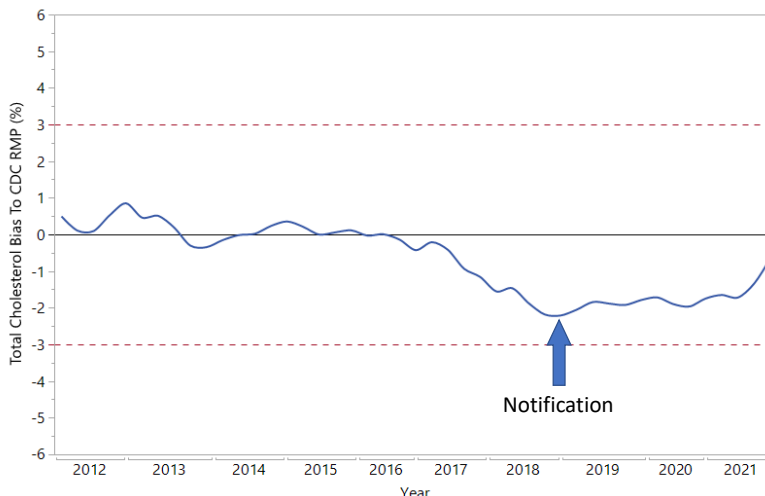


Figure 1: LSP total cholesterol overtime data, showing the recent negative bias trend and improvement.

Recent Partner Engagement and Collaborations

As part of the efforts to ensure accurate and reliable clinical laboratory testing for specific chronic diseases, CSP continues its engagement and coordination with national and international stakeholders:

- CDC and the **College of American Pathologists (CAP)** are supporting the efforts of the only [accuracy-based proficiency testing program](#) in the U.S. CDC will continue to assign reference values to the CAP Proficiency Testing commutable materials used in more than 600 clinical laboratories. Data obtained through this collaboration will support early identification of subtle changes in measurement of accuracy before accuracy changes can have a negative impact on clinical decision making.
- CDC and the French metrological institute **Laboratoire national de métrologie et d'essais (LNE)**: LNE is an active participant in the [CDC Cholesterol Reference Measurement Network \(CRMLN\)](#) and producer of several certified reference materials for lipids. Collaborative projects between CDC and LNE include evaluation of the differences in measurements by spectrophotometry-based Abell Kendall reference measurement procedure and gas chromatography mass spectrometry-based methods for total cholesterol. The collaboration also involves other international metrological institutions such as Singaporean Health Science Authority (HSA). LNE's activities complements the work conducted as part of the European EMPIR project [CardioMet](#). In line with objectives of CardioMet, LNE actively participates in the international initiative to revise performance criteria for LDL-C and HDL-C assay manufacturers, to address sample-specific bias and accuracy of measurements at the low LDL-C and HDL-C concentrations levels. As well, LNE is supporting the work on apolipoprotein standardization, with developing primary reference materials that will be used to calibrate the candidate reference method developed by the CDC, LUMC and University of Leipzig, for the absolute quantification of a panel of apolipoproteins.

LNE and CDC are developing analytical methods for absolute quantification of steroid hormones and endocrine disruptors. CDC has shared reference materials and is organizing an interlaboratory comparison to generate additional data.

- CDC and the **American Association for Clinical Chemistry (AACC)**: CDC is collaborating on a workstream project to support screening of individuals at risk for cardiovascular diseases in low-middle income countries (LMIC) by improving lipids testing capacity and using point-of-care testing (POCT) devices. CDC and AACC have developed training modules for healthcare professional end users on laboratory quality principles for POCT devices. The goal is to expand patient access to lipid testing in remote areas in the Philippines and Bolivia. Read more [here](#).
- Collaborations with the **Partnership for the Accurate Testing of Hormones (PATH)**: CDC and PATH members developed a training series for endocrinology fellows, early-career providers, and endocrinologists on accurate hormone testing offered by the Endocrine Society. Click [here](#) to learn more about the training series.
- [Partners work to develop reliable pediatric reference intervals](#) - Clinicians, CDC, and the American Association for Clinical Chemistry investigated whether current pediatric reference intervals reflect biological changes during child development. Researchers studied data from scientific literature, commercial laboratory websites, study cohorts, and textbooks. The new study, "**Current State of Pediatric Reference Intervals and the Importance of Correctly Describing the Biochemistry of Child Development**," co-authored by CDC, found that accurate and universal pediatric reference intervals are needed to ensure correct pediatric care. CDC previously developed better adult reference intervals and, in collaboration with clinical partners, aims to create better pediatric reference intervals.

CDC CSP Upcoming Programs & Materials

- **Heart Disease and Cardiovascular Health:** CSP is developing certification/monitoring programs for **non-HDL Cholesterol** and **Lipoprotein(a) [(Lp(a))]**
- **Diabetes and Metabolic Diseases:** CSP is the only lab in the U.S. currently able to provide reference measurements for **Glucose**. As part of the CAP collaboration, CSP provides reference values to the CAP survey materials.
- **Cancers, Hormones, and Endocrine Disorders:** CSP is finalizing its certification program for **Free Thyroxine (FT4)** and is collaborating with **North American Menopausal Society (NAMS)** to develop reference intervals for **Estradiol** in post-menopausal women. If interested, CSP can provide you with these materials.
- **Kidney Disease and Bone Health:** CDC is finalizing development of the **PTH Reference Measurement Procedure**. The RMP will be a top-down method to measure full undigested PTH by Mass Spectrometry.

CDC CSP Available Standardization Programs and Services

CSP improves the diagnosis, treatment, and prevention of diseases through accurate and reliable laboratory measurements. In addition to its standardization programs, CSP assists laboratories and assay manufacturers with investigations of potential sources of bias and other imprecision and provides serum products that help with further assessments of analytical assay performance.

<i>CSP assists laboratories and assay developers with calibration and assessment of assay performance</i>	
Program	Analytes
Hormone Standardization (HoSt) Programs	Total Testosterone, Estradiol, Free Thyroxine (New)
Vitamin D Standardization-Certification Program (VDSCP)	Total 25-hydroxyvitamin D
Cholesterol Reference Method Laboratory Network (CRMLN)	Total Cholesterol, Total Glycerides, HDL-C, LDL-C

<i>CSP enables laboratories and investigators to continuously monitor the accuracy of measurements in patient care and research studies over time</i>	
Program	Analytes
CDC Lipid Standardization Programs (LSP)	Total Cholesterol, Total Glycerides, HDL-Cholesterol, Apolipoprotein A1, Apolipoprotein B, (New): Lp(a), non-HDL
CDC Accuracy-based Monitoring Programs (AMP)	Total 25-hydroxyvitamin D, Total Testosterone

<i>Method Verification Samples and Analytes</i>
CDC offers up to 120 different samples for more detailed method verification and characterization for Total 25-hydroxyvitamin D, Total Testosterone, and Estradiol. We also offer orientation values of additional steroid hormones (17 α -Hydroxyprogesterone, 17-OHP Androstenedione, Progesterone, Testosterone, Estrone, 17 β -Estradiol, Estrone sulfate, and Dehydroepiandrosterone sulfate), C3-epi-25-hydroxyvitamin D ₃ , and 24,25-Dihydroxyvitamin D ₃ . Customization is available upon request.

Upcoming Events of Interest

Please check event websites for updated information.

CSP will present virtually and in-person at upcoming scientific meetings and events. Presentations will cover related CDC-related programs and activities:

- **June 11 - 14, 2022: ENDO 2022 [Annual Conference](#)**, Atlanta, GA -USA
- **June 26 - 30, 2022: IFCC WorldLab Congresses [Conference](#)**, Seoul, South Korea
- **July 24 - 28, 2022: AACC Annual Scientific Meeting & Clinical Lab Expo 2022**, Chicago, IL – USA
CSP will provide presentations during CDC forum and brown bag sessions at the [AACC Annual Meeting](#)
- **SAVE THE DATE: Thursday, October 13, 2022, 10:00AM**
CDC Clinical Standardization Programs Virtual Forum 2022
Join us to learn more about our programs and services and new programs in development.
More details to follow.
- **November 5-7, 2022 - [American Heart Association](#) Scientific Sessions 2022**, Chicago, IL - USA

Latest List of Newly Certified Participants for CDC HoSt, VDSCP, AMP and LSP

➤ **Organizations successfully within criteria for CDC Accuracy-based Monitoring Program (CDC AMP)**

**List of AMP Participants that are within performance criteria for 2019-2022 is attached.*

➤ **New Assays/Organizations certified for CDC HoSt, VDSCP and CRMLN**

University Hospital – Biochemistry Laboratory, Grenoble, France	LC/MS/MS assay, 2D LC METHODE (Vitamin D)
Department of Obstetrics and Gynecology, The University of Hong Kong, Hong Kong, China	Immunoassay (Vitamin D)
Centre Hospitalier Universitaire de Liège, Sart-Tilman, Belgium	LC/MS/MS (Estradiol)
Sekisui Medical Co., Ltd., Tsukuba Plant, Ibaraki, Japan	(Total Glycerides)
UMA Co., Ltd., Chiba, Japan	(Total Glycerides)
FUJIFILM Wako Pure Chemical Corporation, Diagnostics Research Laboratories, Hyogo, Japan	(Total Glycerides)

➤ **Complete List of all Certified Participants:**

CDC HoSt and VDSCP: https://www.cdc.gov/labstandards/hs_certified_participants.html (website updated quarterly).

Blood Lipids:

CRMLN- Certified Manufacturers: https://www.cdc.gov/labstandards/crmln_certified_manufacturers.html

CRMLN- Certified Clinical Laboratories: https://www.cdc.gov/labstandards/crmln_certified_laboratories.html

CDC LSP- List of Certified Participant: https://www.cdc.gov/labstandards/lsp_participants.html

Continuous evaluation and certification help ensure that your assay's performance is consistently of high quality.

For more information or to enroll in our Standardization Programs, contact us at:

CDC AMP/HoSt and VDSCP: Standardization@cdc.gov

LSP and CRMLN: cdclsp@cdc.gov

Website: <https://www.cdc.gov/labstandards/index.html>

The findings and conclusions in this update are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry. Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.