CDC's Clinical Standardization Programs (CDC CSP): Ensuring the Accuracy and Reliability of Chronic Disease Biomarker Tests

Hubert W. Vesper, Ph.D.

Director, CDC Clinical Standardization Programs

Clinical Chemistry Branch

Division of Laboratory Sciences, NCEH

The analytical accuracy and reliability of biomarkers used in patient care and public health have raised concerns among stakeholders

IOM 2011

"A single individual might be deemed deficient or sufficient *[for vitamin D]* depending on the laboratory where the blood is tested."

Endocrine Society JCEM 2010;95:4541-48

"deficiencies in these *[testosterone]* assays limit their broad and effective implementation and threaten the health of those patients whose medical care relies upon its accurate measurement"

Endocrine Society JCEM 2013;98:1376-87

"Breast cancer, diseases of bone, cognitive dysfunction, and cardiovascular disease are among those that suffer from a limited ability to combine data from diverse studies because measurements and standards *[of estradiol]* are not uniform."

Variability in vitamin D measurements may cause incorrect patient classification

CAP Accuracy-based Vitamin D Survey – 2019

Method/Assay	Median (ng/mL)	Lowest reported Value (ng/mL)	Highest Reported Value (ng/mL)
Assay 1	29.8	26.1	32.0
Assay 2	30.6	26.0	33.3
Assay 3	32.0	24.0	37.1
Assay 4	28.0	26.8	40.7
Assay 5	32.3	26.0	37.5
Assay 6	30.0	25.3	39.1
Assay 7	37.8	26.6	46.0
Assay 8	32.6	28.5	38.0
Assay 9	31.4	24.9	38.4
Assay 10	34.0	26.0	45.4
Assay 11	30.9	26.0	41.9

Indicates insufficient Vitamin D status based on Endocrine Society Guideline

Reference Value 36.70

True value

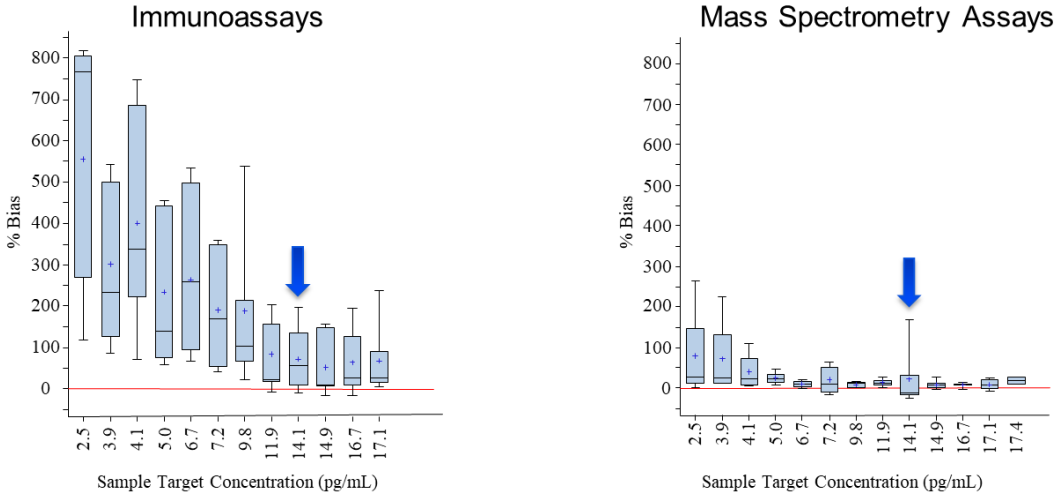
Sufficient Vitamin D status

Based on Endocrine Society Guideline

Variability in estradiol measurements prevent consistent diagnosis of patients

Example:
European Menopause and Andropause Society recommends a cut-off of 14 pg/mL to confirm diagnosis of premature ovarian failure

Bias distributions among assays for samples with reference values ranging between 2.8 – 17.4 pg/mL)

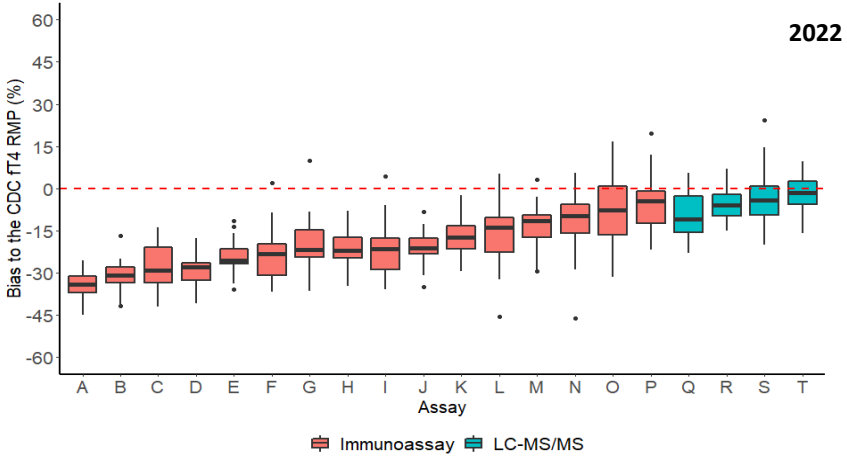


Values reported for a sample with a target value of 14.1 pg/mL ranged from 9.4 to 64.8 pg/mL

Vesper et al. Steroids 2014;82:7-13

Very high differences in analytical accuracy of FT4 assays may cause inconsistent diagnosis

Distribution of bias observed with 20 assays



2022 CDC Interlaboratory comparison study

- Data suggest inconsistent calibration being the main source of measurement bias among assays
- Alignment to the CDC/IFCC reference method can be achieved with immunoassays and mass spectrometry-based assays

Several tests in need of standardization are highly utilized in patient care

Several tests in need of improvements
are among top 20 based on Medicare payments

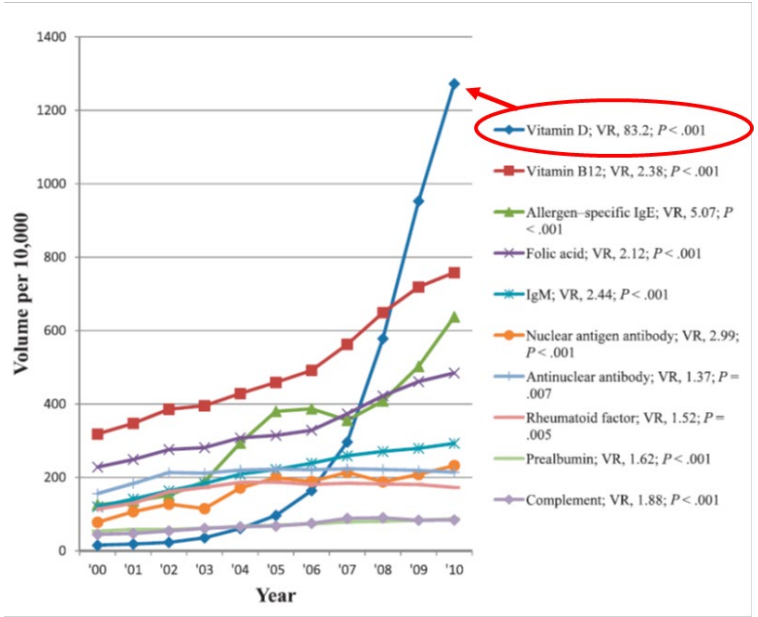
Top 20 lab tests based on Medicare Part B payments in 2016

	Test Description (Procedure Code)*	Number of Tests (Millions)	Medicare Payments (Millions)
1.	Blood test, thyroid-stimulating hormone (TSH) (84443)	21.5	$482
2.	Blood test, comprehensive group of blood chemicals (80053)	41.6	$470
3.	Complete blood cell count (red blood cells, white blood cells, platelets) and automated differential white blood cell count (85025)	42.0	$433
4.	Blood test, lipids (cholesterol and triglycerides) (80061)	29.0	$411
5.	Vitamin D_3 level (82306)	9.0	$350
6.	Hemoglobin A1C level (83036)	19.3	$250
7.	Drug test(s), definitive, per day, 22 or more drug class(es), including metabolite(s) if performed (G0483)	1.2	$241
8.	Drug test(s), presumptive, any number of drug classes, per date of service (G0479)	3.0	$221
9.	Blood test, basic group of blood chemicals (80048)	13.7	$133
10.	Drug test(s), definitive, per day, 15–21 drug class(es), including metabolite(s) if performed (G0482)	0.8	$127
11.	Parathormone (parathyroid hormone) level (83970)	2.2	$120
12.	Cyanocobalamin (vitamin B_{12}) level (82607)	5.6	$113
13.	Blood test, clotting time (85610)	19.6	$105
14.	PSA (prostate specific antigen) measurement (84153)	4.2	$103
15.	Thyroxine (thyroid chemical) measurement (84439)	7.1	$85
16.	Bacterial colony count, urine (87086)	7.6	$82
17.	Drug test(s), definitive, per day, 8–14 drug class(es), including metabolite(s) if performed (G0481)	0.6	$73
18.	Natriuretic peptide (heart and blood vessel protein) level (83880)	1.5	$69
19.	Drug test(s), definitive, per day, 1–7 drug class(es), including metabolite(s) if performed (G0480)	1.0	$69
20.	Ferritin (blood protein) level (82728)	3.7	$67

Analytes addressed in CDC CSP

Source: OEI-09-17-00140

The number of vitamin D tests reimbursed by Medicare increased over 80-fold between 2000 and 2010



Arch Pathol Lab Med. 2014;138:189–203

CDC CSP improve diagnosis, treatment, and prevention of selected diseases by standardizing clinical laboratory measurements

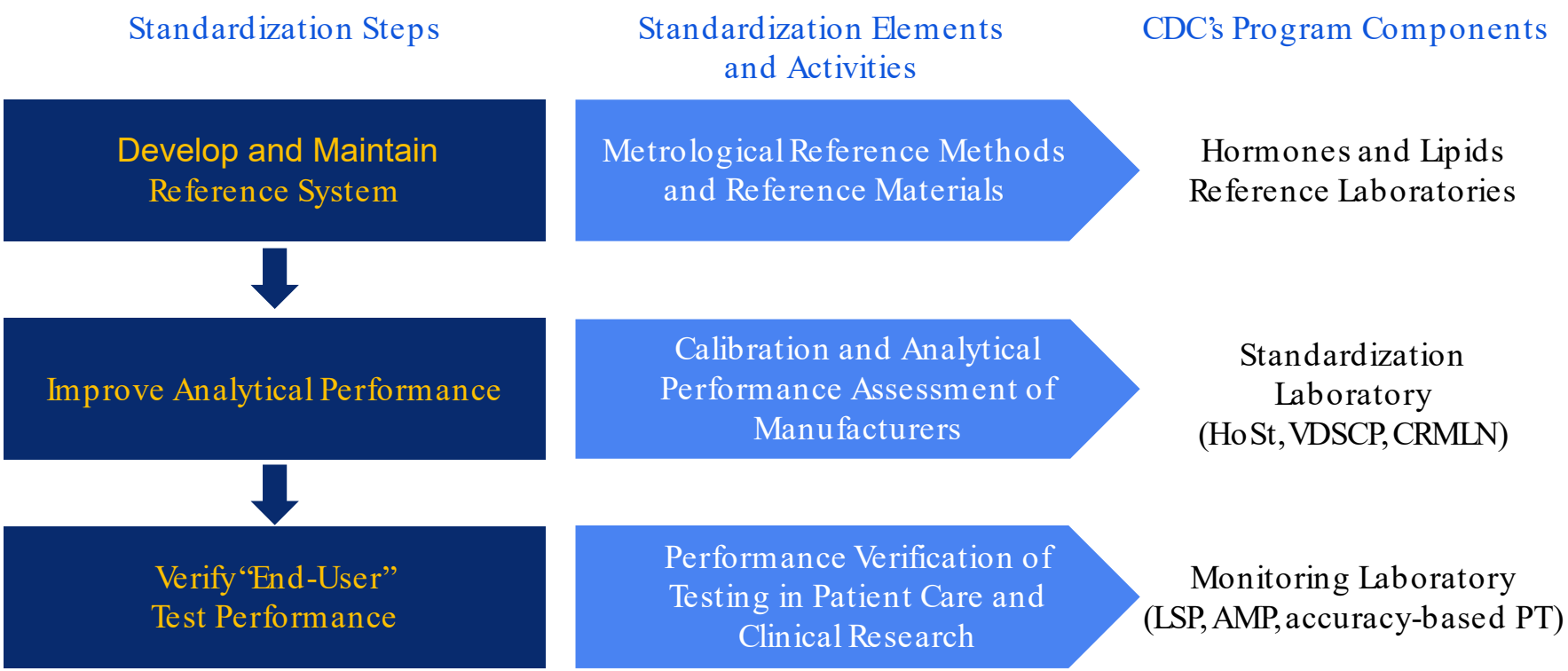
Objective

Create measurement results with measurement procedures of appropriate analytical performance that are traceable to one accuracy basis, and therefore are comparable across methods, location, and over time

CDC standardized laboratory test
has demonstrated through a thorough, independent assessment that its analytical performance meets relevant analytical performance goals derived from clinical needs

Standardization is an ongoing process
in which relevant analytical performance parameters of a laboratory test are improved and maintained to meet certain clinical needs

CDC's Clinical Standardization Programs provide unique services at every step in the standardization process



CDC's Clinical Reference Laboratories (CRL) continuously operate 10 reference methods

Reference Measurement Procedures operated at CDC CSP

Analyte	Method Principle	Performance Requirements Bias	Imprecision
Total Cholesterol	ID-GC-MS	± 1%	≤ 1%
	Spectrophotometry	± 1%	≤ 1%
Total Glycerides	ID-GC-MS	± 2.55 %	≤ 3.95%
HDL-C	Ultracentrifugation-Spectrophotometry	± 2%	≤ 1.5%
LDL-C	Ultracentrifugation-Spectrophotometry	± 1 mg/dL	≤ 1 mg/dL
Testosterone*	UPLC-MS/MS	±5.7 %	≤ 2.8 %
Estradiol*	UPLC-MS/MS	±5 %	≤ 2.1 %
25-OH-Vitamin D2* 25-OH-Vitamin D3*	UPLC-MS/MS	±5.7 %	≤ 2.8 %
Free Thyroxine*	Equilibrium Dialysis-UPLC/MS/MS	±2.5%	≤5%
Glucose*	GC-MS	±1%	≤ 2%

* CDC CSP is the only laboratory in the U.S. continuously operating these RMPs

- All RMPs were reviewed for compliance with relevant ISO standards (JCTLM)
- CDC CRL ISO 15195 (Calibration Laboratory) accredited
- CDC's CRL performs ~200 reference value assignments per year

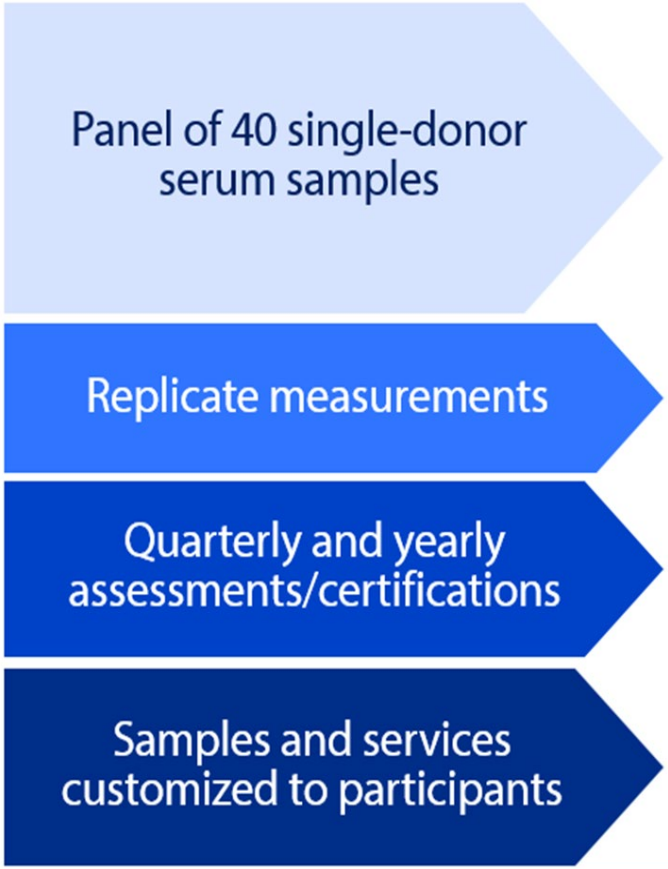
Reference measurement procedures in development

- Parathyroid Hormone by LC/MS/MS
- Lp(a) by LC/MS/MS
- Free testosterone by ED-LC/MS/MS

CDC CRL assists organizations with developing RMPs and with building reference laboratory capacity, for example:

- IFCC RMP development for Lp(a)
- Korea Disease Control and Prevention Agency reference lab development

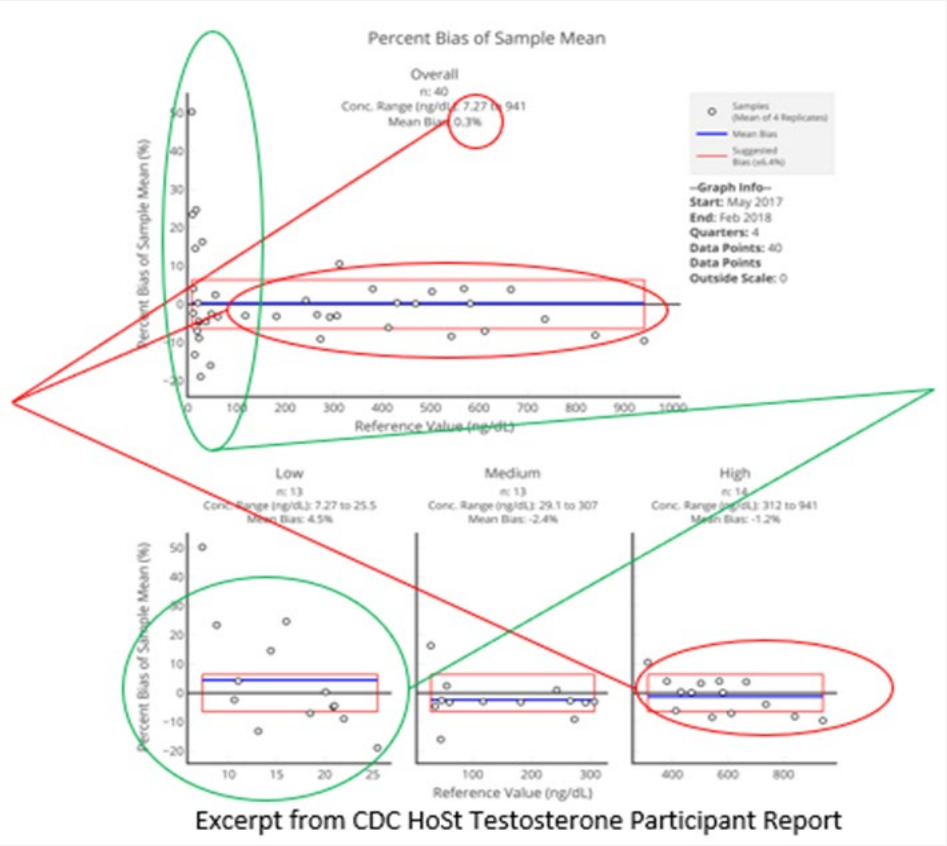
CDC CSP certification programs provide detailed information not available with other programs



- Enables thorough evaluation of measurement performance across relevant concentration ranges
- Allows for identification of sources of bias (i.e., calibration vs. non-specificity)
- Avoids potential problems related to commutability frequently observed in pooled/altered serum
- Provides information on imprecision in addition to bias
- Provides information about performance over time
- Allows timely detection of changes in accuracy
- Customization of sample concentration to cover reportable range
- Individual review of data to minimize non-analytical sources of error (i.e., clerical errors with data input)

CDC CSP provide detailed information to participants about the analytical performance across the analytical measurement range

Assay appears to be sufficiently well calibrated as indicated in the mean bias and bias patterns (especially at high analyte concentrations)



Excerpt from CDC HoSt Testosterone Participant Report

Assay appears to be affected by interfering compounds and analyte recovery, as indicated in bias patters at low analyte concentrations
(mainly samples from female donors)

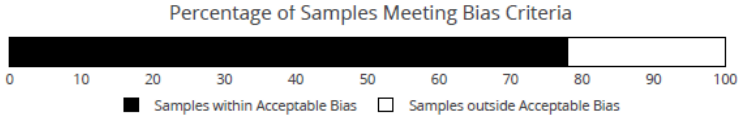
CDC's Clinical Standardization Programs provide detailed information about measurement performance to its participants and the public

Excerpt from CDC VDSCP Participant Report

Bias Evaluation by Concentration Range

	n	Conc. Range (nmol/L)	Bias (%)* Mean	SD	Median	95% CI	Min	Max	Percentage of Samples Meeting Bias Criteria
Reference Concentration Range									
Low	13	10.4 to 60.5	7.3	9.1	4.9	1.8 to 12.8	-1.1	34.0	54
Med	13	60.9 to 96.1	1.5	3.3	2.1	-0.5 to 3.5	-4.2	6.9	92
High	14	99.4 to 183	1.3	3.4	0.3	-0.6 to 3.3	-3.7	8.0	86
Total									
Overall	40	10.4 to 183	3.3	6.3	2.6	1.3 to 5.4	-4.2	34.0	78

* Evaluation was made using individual sample biases in each partition type



Excerpt from CDC Website

https://www.cdc.gov/labstandards/pdf/hs/CDC_Certified_Vitamin_D_Assays-508.pdf

Table 1: Currently Certified Assays

Participant	Measurement Principle	Assay Identifier	Assay Measurement Range (nmol/L)	Certification Measurement Range (nmol/L)	Certification Date *(active for 1 quarter)*	Individual Samples Pass Rate (%)	Participant's Contact Information

A certified assay meets the mean bias "calibration bias") criterion

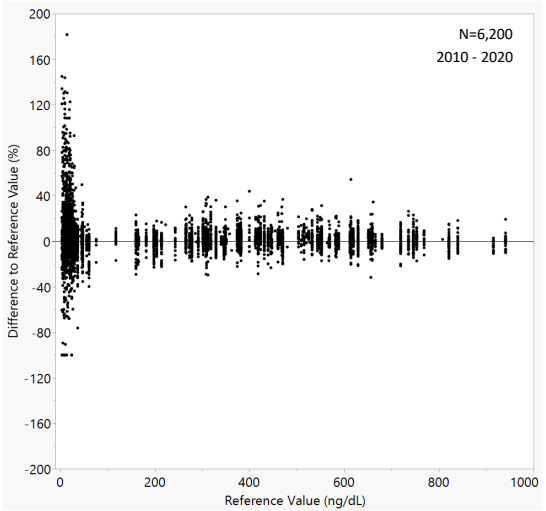
Mean bias calculated using 40 samples measured over 4 consecutive quarters

Proportion of individual samples meeting bias criterion ("reliability" of results obtained on individual samples)

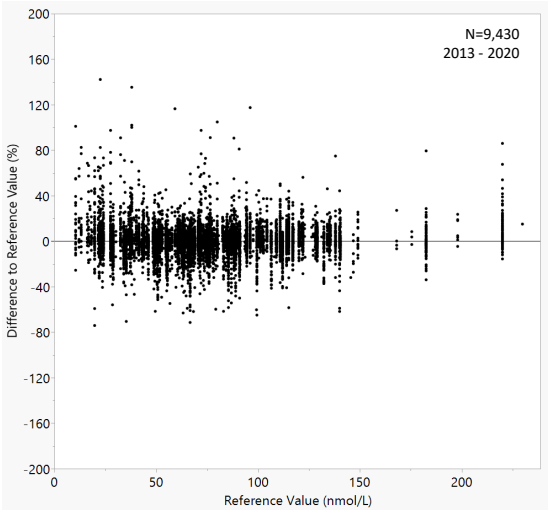
CDC's CSP data indicate consistent assay calibration is not always sufficient for improving the accuracy and reliability of measurement results

Bias patterns of individual donor samples for three key analytes obtained from CDC CSP participants (certified and non-certified)

Testosterone

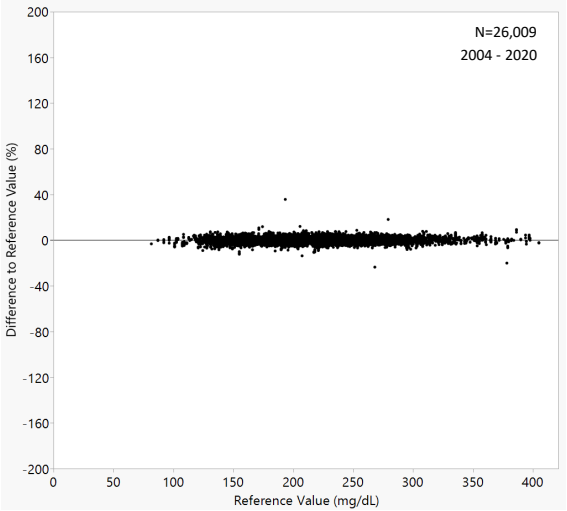


25-OH-Vitamin D



Each dot represents the mean of 4 measurements

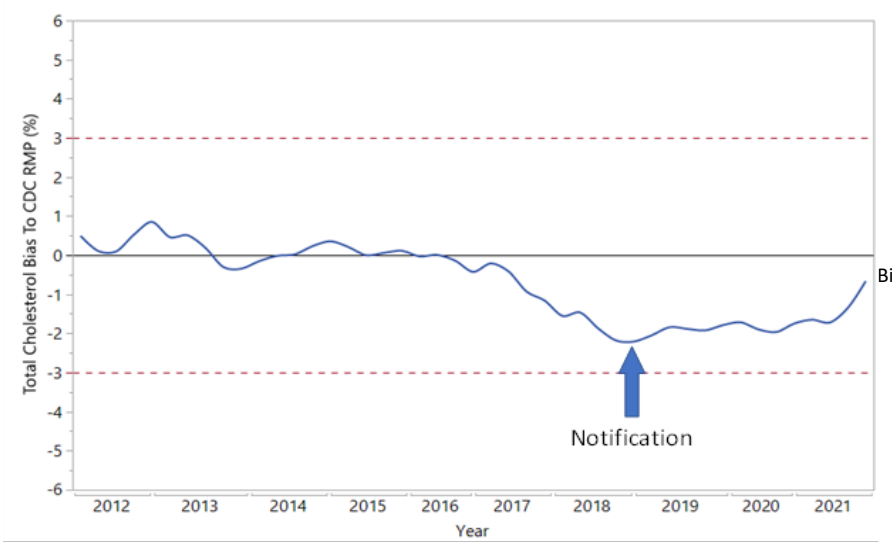
Total Cholesterol



Procedures and approaches to improve and maintain measurement accuracy and reliability need to extend beyond re-calibration activities.
These activities need to be customized for each analyte.

CDC CSP monitor analytical performance of its participants to detect and address trends in a timely manner

Total cholesterol bias to RMP observed with one manufacturer in the CDC LSP program

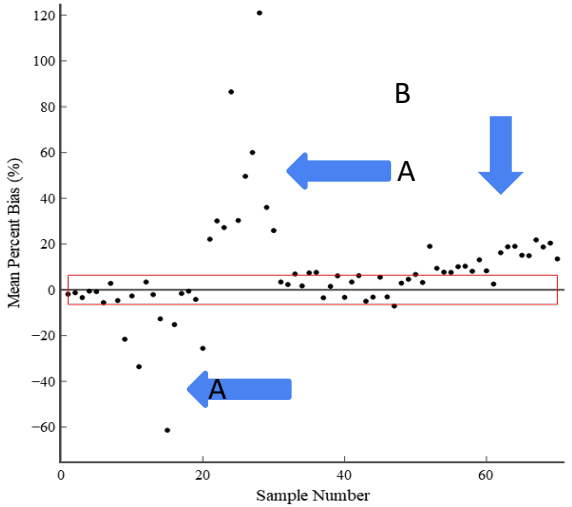


Manufacturer was notified which helped prevent bias to move outside limits

Line represents the mean bias from approx. 600 data points across a year collected from 50 laboratories

Bias Limits

Total testosterone bias to RMP observed with one CDC HoSt participant over 7 quarters

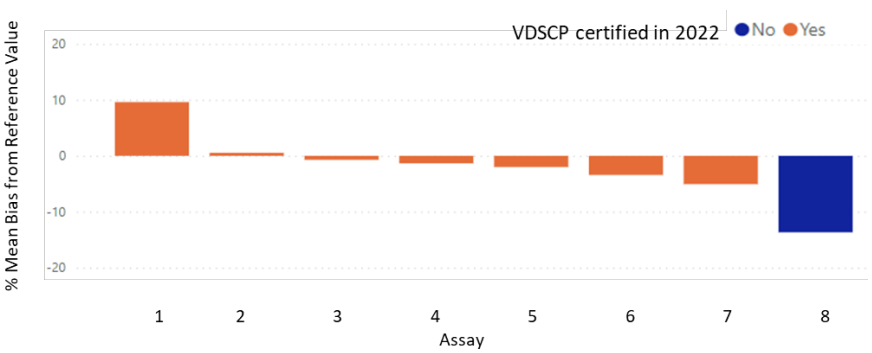


Quarterly reports helped participant identify problems with assay operation (A) and calibration (B)

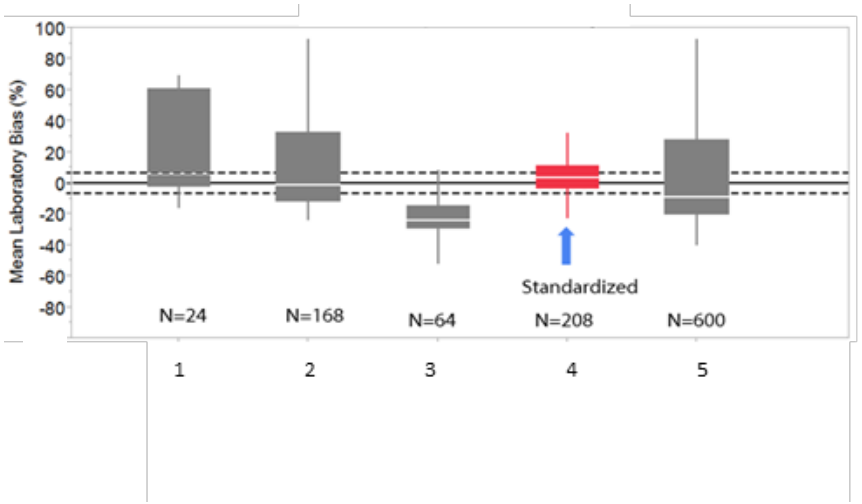
Each dot represents the mean of 4 replicate measurements

VDSCP certified assays show higher accuracy than non-certified assays

Peer group mean bias of 6 survey samples in the 2022 CAP Accuracy Based Vitamin D Survey

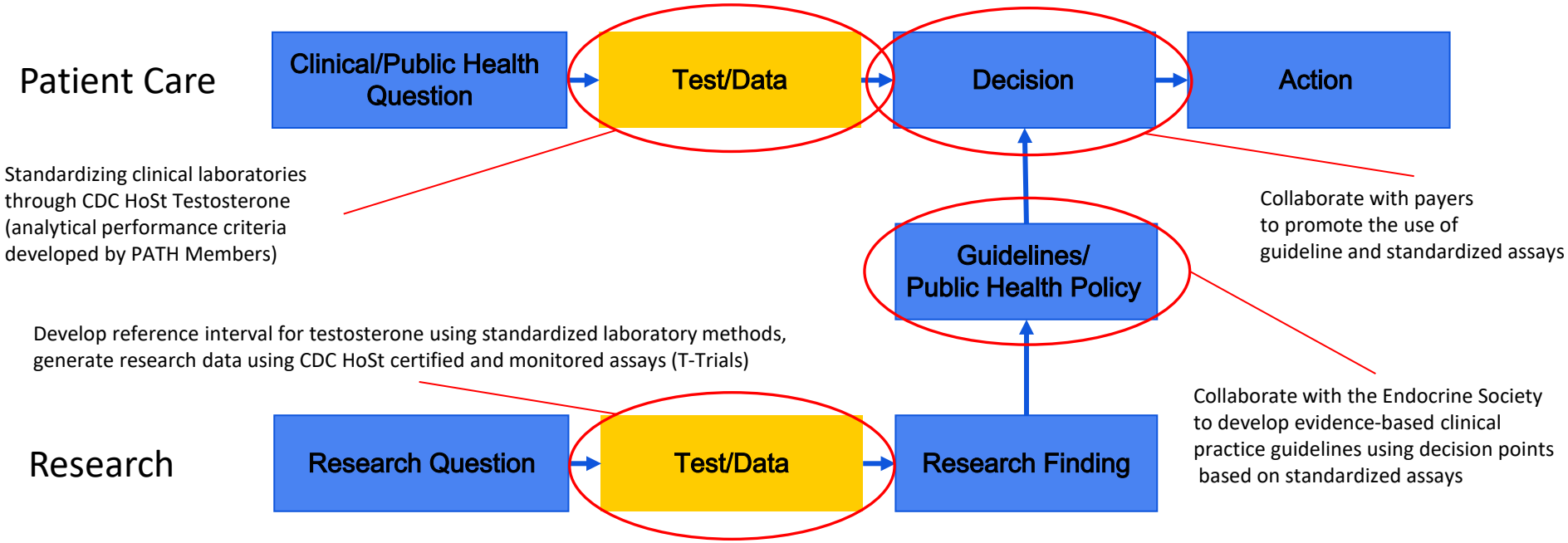


Bias distribution of samples used in the New York State Department of Health EQA/PT Survey



CDC CSPs participation is voluntary. Currently standardized and non-standardized tests are used in patient care and public health

CDC CSP collaborate with stakeholders to ensure quality in every step of the evidence-based decision-making process



Summary

- CDC Clinical Standardization Programs (CDC CSP) assist IVD manufacturers and laboratories with improving and monitoring analytical performance
- CDC CSP laboratories comply with international standards of metrology and use well-established evaluation protocols
- Establishing only correct assay calibration may not be sufficient to meet clinical needs, CDC CSP works with participants on improving all relevant performance parameters
- Certification programs and accuracy-based monitoring programs provide important, complementary information to IVD manufactures and laboratories
- Participation in CDC's clinical standardization programs is voluntary. Therefore, standardized and non-standardized assays are used in patient care without distinction. CDC CSP is collaborating with stakeholders to educate the laboratory communities about the importance of assay standardization.

Thank you!

For further information about CDC CSPs, please contact: standardization@cdc.gov

Hubert W. Vesper, PhD
Director, Clinical Standardization Programs
hvesper@cdc.gov

For more information, contact NCEH/ATSDR
1-800-CDC-INFO (232-4636)
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