CDC’s Clinical Standardization Programs

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December 1, 2015, JCTLM Members’ and Stakeholders’ Meeting
Sevres, France
CDC Standardization Programs address clinical and public health needs for accurate and reliable measurements

- **Endocrine Society** JCEM 2010;95:4541-48
  “deficiencies in these (testosterone) assays…threaten the health of those patients whose medical care relies upon its accurate measurement”

  “This (inaccuracy in testosterone tests) leads to diagnostic and management dilemmas…”

- **Endocrine Society** JCEM 2013;98:1376-87
  “the care of patients across the life span is hampered by the lack of availability of sensitive, precise, and specific estradiol assays.”

- **Institute of Medicine** 2011
  “A single individual might be deemed (vitamin D) deficient or sufficient, depending on the laboratory where the blood is tested.”
CDC’s Clinical Standardization Programs improve the laboratory diagnosis and detection of selected chronic diseases

Program Goals:

- Improve the accuracy of laboratory measurements for selected disease biomarkers
- Provide technical support to agencies and organizations working to improve the accuracy and reliability of clinical laboratory measurements
CDC’s programs perform each step in the standardization process to effectively improve laboratory measurements.

**REFERENCE LABORATORY SERVICES**
Provide reference value assignments to materials used in clinical and research laboratories.

**STANDARDIZATION SERVICES**
Assist individual participants with calibration and maintenance of accuracy.

**PERFORMANCE MONITORING SERVICES**
Assess measurement performance in patient care and research.
CDC’s programs perform each step in the standardization process to effectively improve laboratory measurements.

- **Develop and Maintain Reference System**: Target value assignments by Hormones, Vitamin D and Lipid Reference Laboratories incl. Cholesterol Reference Method Laboratory Network (CRMLN).
- **Establish Metrological Traceability**: Certification of performance through HoSt, VDSCP, and CRMLN.
- **Verify “End-User” Test Performance**: Performance monitoring through Lipids Standardization Program (LSP), accuracy-based EQA/PT programs, accuracy-based blind QCs in research studies.
CDC operates several reference measurement procedures and continuously develops new procedures.

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Methodology</th>
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<tbody>
<tr>
<td>Testosterone</td>
<td>HPLC/MS/MS</td>
</tr>
<tr>
<td>Estradiol</td>
<td>HPLC/MS/MS</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D</td>
<td>HPLC/MS/MS</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>GC/MS and Abel Kendall</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>GC/MS</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>UC/Abel Kendall</td>
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<tr>
<td>LDL-Cholesterol</td>
<td>UC/Abel Kendall</td>
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<tr>
<td>Glucose</td>
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<tr>
<td>Thyroid Hormones</td>
<td>UPLC/MS/MS in development</td>
</tr>
<tr>
<td>Parathyroid Hormone</td>
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</tbody>
</table>
CDC reference laboratory assigns target values to over 200 sera per year

Average annual number of sera with target values by analyte

Blood Lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides
Vitamin D: 25-OH-Vitamin D3, 25-OH-Vitamin D2
Cholesterol Reference Method Laboratory Network (CRMLN) maintains highly accurate and precise reference measurements for over 10 years.
CDC Performance Certification Programs are performed with individual donor specimens

CDC suggests a two phase process for performance evaluation and certification

**Phase 1**
Performance assessment and adjustment using single-donor samples with known reference values

**Phase 2**

- HoSt and VDSCP:
  Quarterly performance monitoring with 10 blinded single-donor samples provided by CDC

- CRMLN:
  Performance assessment with at least 40 single-donor samples provided by the manufacturer

Performance evaluation based on CLSI document EP 9 using performance criteria suggest by the clinical and laboratory communities
**CDC Standardization Programs** provide unique services to support laboratories improve measurement performance

**CDC HoSt Program and VDSCP**

| Panel of 40 single-donor serum samples | • Avoids potential problems related to commutability frequently observed in pooled/altered serum  
|                                      | • Enables thorough evaluation of measurement performance across relevant concentration ranges  
|                                      | • Allows for identification of the sources for bias (calibration vs. non-specificity) |
| Replicate measurements               | • Provides information on imprecision in addition to bias |
| Quarterly and yearly assessments/certifications | • Allows timely detection of changes in accuracy (quarterly)  
|                                          | • Verifies performance over time (yearly) |
| Support to participants               | • Minimizes other sources of error (i.e. clerical errors)  
|                                          | • Customization of analyte concentration to cover the reportable range of the assay |
CDC’s Standardization Programs is increasing in size and scope

Participation in the CRMLN Certification remained constant over the past 5 years

Average Annual Participation:
Manufacturers: 37
Systems/Assays: 110
Laboratories: 200

CDC’s Standardization Programs issue over 1,000 performance evaluations each year
Calibration bias of testosterone measurements improved since the start of the CDC HoSt Program

*MS assays only*
Calibration bias of estradiol measurements improved since the start of the CDC HoSt-Estradiol Program

- 2012 E2 Interlaboratory Study (n=17)
- 2014 E2 HoSt (n=11)
CDC supports PT/EQA providers with their surveys and monitors measurement performance of survey participants.

CDC is assigning target values for accuracy-based PT/EQA surveys conducted by the following organizations:

- College of American Pathologist (CAP)
- Royal College of Pathologists of Australasia (RCPA)
- New York State Department of Health
Total and HDL-cholesterol measurements performed in patient care are highly accurate with very small variability.

**CAP ABL Survey Bias Distribution by Year**

### Total Cholesterol
- **2010**
  - Median: 0.0
  - IQR: 3.2
  - N: 1,089
- **2011**
  - Median: 0.2
  - IQR: 3.2
  - N: 1,130
- **2012**
  - Median: -0.1
  - IQR: 3.3
  - N: 1,167

### HDL-Cholesterol
- **2010**
  - Median: -3.3
  - IQR: 10.3
  - N: 1,087
- **2011**
  - Median: -1.6
  - IQR: 8.5
  - N: 1,133
- **2012**
  - Median: -1.4
  - IQR: 7.9
  - N: 1,161

Interquartile range is well within the total allowable error of 7.9%

Interquartile range is well within the total allowable error of 11.6%
Certification of manufacturers leads to improved measurement accuracy in patient care.

Absolute mean bias observed in CAP-ABVD samples measured by several clinical laboratories using the same immunoassay.

<table>
<thead>
<tr>
<th>Year and Survey</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>2012-A</td>
<td>59</td>
</tr>
<tr>
<td>2012-B</td>
<td>52</td>
</tr>
<tr>
<td>2013-A</td>
<td>85</td>
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<tr>
<td>2013-B</td>
<td>93</td>
</tr>
<tr>
<td>2014-A</td>
<td>98</td>
</tr>
<tr>
<td>2014-B</td>
<td>93</td>
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Start of Enrollment by Manufacturer

1st Manufacturer Certification
CDC Standardization Program continues to improve clinical laboratory testing by increasing its program activities

- Provide new panels of 120 individual single-donor samples with reference target values for advanced performance testing
- Include individual sample bias in addition to overall mean bias in performance evaluation
- Add samples from patients with certain diseases to sample sets used in performance evaluation
- Conduct ad-hoc interlaboratory and commutability studies using the CDC Standardization Programs infrastructure
CDC supports other organizations working on improving the accuracy and reliability of clinical tests

<table>
<thead>
<tr>
<th>Organization</th>
<th>Project/Activity</th>
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<tr>
<td>International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)</td>
<td>Standardization of Parathyroid Hormone</td>
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<td></td>
<td>Guideline Development (Commutability)</td>
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<tr>
<td>National Glycohemoglobin Standardization Program (NGSP)</td>
<td>Standardization of HbA1c</td>
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<tr>
<td>Diabetes Technology Society (DTS)</td>
<td>Post-market Surveillance Program for Glucose Monitors</td>
</tr>
<tr>
<td>Clinical and Laboratory Standards Institute (CLSI) and International Standards Organization</td>
<td>Standards and Guideline Development</td>
</tr>
<tr>
<td>JCTLM and National Institute for Standards and Technology (NIST)</td>
<td>Reference Systems</td>
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<tr>
<td>American Association of Clinical Chemistry</td>
<td>Harmonization Initiative</td>
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<td>Universal Sample Bank Project</td>
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Partnership for the Accurate Testing of Hormones (PATH) supports and promotes standardized hormone tests for better healthcare and research.

PATH is a stakeholder organization

- Consists of clinical, medical, and public health organizations
- Promotes accurate tests and appropriate use of hormone tests through
  - Education
  - Advocacy
  - Technical Support

www.hormoneassays.org
Acknowledgments

Collaborators:

Drs. Linda Thienpont and Katleen Van Uytfanghe, University of Ghent
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