VDSP – Standardisation Issues with 25-hydroxyvitamin D

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For the Vitamin D Standardization Program (VDSP)

Vitamin D: Analytical and Clinical Stories
7th July 2016
Imperial College, South Kensington Campus
London, UK
Thank you!

• I would like to thank Dr. Walker for her kind introduction.

• I would like to thank Graham Carter and all of the meeting organizers for their kind invitation.

• Finally, I would like to thank, as well, Graham, Julia and Emma for their support of the Vitamin D Standardization Program (VDSP).
Vitamin D Metabolism and Tissue Homeostasis

Vitamin D (Prohormone)

- Diet + UV:
  - Liver
  - Prohormone 25(OH)D
    - Kidney
      - Active Hormone 1α-hydroxylase
      - 1,25(OH)2D
        - Bone Health
        - (Endocrine)
        - Increased Calcium Absorption

- Milk
  - Liver
  - Prohormone 25(OH)D
  - Kidney
    - Active Hormone 1α-hydroxylase
    - 1,25(OH)2D
      - Bone Health
      - (Endocrine)
      - Increased Calcium Absorption
Vitamin D Status Measurement

Total 25-Hydroxyvitamin D or 25(OH)D

• Total 25(OH)D is defined as

\[ \text{Total 25(OH)D} = 25(\text{OH})D_2 + 25(\text{OH})D_3^* \]

• Units: ng/mL or nmol/L where:

\[ \text{ng/mL} \times 2.5 \approx \text{nmol/L} \]

* Assumes that Vitamin \(D_2\) and \(D_3\) are of equal biological value.
Outline

- Chaos
- Vitamin D Standardization Program (VDSP)
- Going Forward
Huge numbers of people either are, or are not vitamin D deficient

This deficiency either is, or is not, causing disease thereby reducing quality and quantity of life

The vitamin D field is in chaos…….
How Can Patients, Physicians & Policy Makers NOT be Confused?
Source of Chaos: The Problem

Assay Variation Confounds the Diagnosis of Hypovitaminosis D: A Call for Standardization


What is Standardization?

Standardized laboratory measurement of 25-hydroxyvitamin D is:

**Accurate and comparable to Gold Standard Reference Measurement Procedures (RMPs)**

over time, location, and laboratory procedure.

All Laboratories report *true* value – based on NIST, Ghent & CDC RMPs which permits:

- Pooling of research results
- Evidenced-based guidelines
- Informed decision making by physicians, policymakers and others
Trends in Original and Standardized 25(OH)D


25-hydroxyvitamin D (nmol/L)
Trends in Original and Standardized 25(OH)D

- 1988-1994
- 2001-2002
- 2003-2004
- 2005-2006
Vitamin D Standardization Program (VDSP): An Overview
Vitamin D Standardization Program (VDSP)*

Goal: Promote the standardized laboratory measurement of 25-hydroxyvitamin D – a measure of vitamin D status – in order to improve clinical and public health practice worldwide.


Note: 25-hydroxyvitamin D is abbreviated as 25(OH)D
VDSP Reference Measurement System Components

- NIST, Ghent & CDC RMPs
- NIST Standard Reference Materials (SRM)
- Performance Standards
- CDC Vitamin D Standardization-Certification Program
- Accuracy-Based Performance Testing (PT)
- Standardizing completed studies
VDSP: Steps to Standardization

1. Develop Reference Measurement System
3. Calibrate Individual Clinical & Research Laboratory Assays to Reference Methods
4. Verify End-User Test Performance

Reference Methods, Reference Materials, Certification Program, Accuracy-based PT/EQA
NIST SRMs, CDC VDSCP, Single Donor Serum Panel
NIST SRMs, CAP, DEQAS PT/EQA & NIST-NIH VitDQAP
CDC VDSCP, CAP ABVD, DEQAS
VDSP: Calibration of Individual Assays

Reference procedure (LC-IDMS or GC-IDMS)

Reference Laboratories

Primary Calibrator

Calibration

RMP Value
Assigned Patient Samples

Calibration

Commutable SRM

Assay Manufacturer

Accuracy-Based
PT/EQA

Commutable Samples

Clinical Laboratory

* Adapted from: Myers G. Steroids 2008;73:1293-1296
## VDSP Performance Limits Based on Biological Variation*

<table>
<thead>
<tr>
<th>Measurements</th>
<th>CV (%)</th>
<th>Mean Bias (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Labs</td>
<td>≤ 5%</td>
<td>≤ 1.7%</td>
</tr>
<tr>
<td>“Routine” Labs</td>
<td>≤ 10%</td>
<td>≤ 5%</td>
</tr>
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</table>

VDSP: Calibration of Individual Assays

Reference procedure (LC-IDMS or GC-IDMS)
Reference Laboratories

Calibration

CDC Standardization-Certification Program

Calibration

NIST SRM 927a & 2972

Accuracy-Based PT/EQA

CAP ABVD and DEQAS

Assay Manufacturer

Clinical Laboratory

Primary Calibrator

* Adapted from: Myers G. Steroids 2008;73:1293-1296
VDSP: Calibration of In-House Assays

- Reference procedure (LC-IDMS or GC-IDMS) Reference Laboratories
  - Primary Calibrator
  - Calibration
    - CDC Standardization-Certification Program
  - Calibration
    - NIST SRM 927a & 2972
  - Accuracy-Based PT/EQA
    - CAP ABVD and DEQAS
- In-House Assay

* Adapted from: Myers G. Steroids 2008;73:1293-1296
Steps You Can Take Now To Achieve Standardization

- Use NIST SRMs to calibrate assays and serum pools, and as trueness controls

- CDC Vitamin D Standardization Certification Program – Participation needed by
  - Commercial assay manufacturers
  - Commercial and large clinical laboratories
  - Research laboratories
Participate in CAP and/or DEQAS accuracy-based EQA programs:
  - Small clinical laboratories
  - Research laboratories

Run serum-based SRM 972a (DEQAS) samples with research study samples – truenessness controls

Use EQA results to monitor accuracy and precision (mean bias) over time
VDSP Performance Limits Based on Biological Variation*

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Laboratory X: DEQAS Results
January 2017 Distribution

Mean Bias = 0%
Laboratory X: DEQAS Results April 2016 - January 2017 Distributions
Going Forward

Certified Laboratories and Assays & Recent Data from DEQAS
## CDC Certified Laboratories as of November 2014

<table>
<thead>
<tr>
<th>N</th>
<th>Participant</th>
<th>Measurement Principle</th>
<th>Method Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DiaSorin</td>
<td>Chemiluminescence Immunoassay</td>
<td>LIAISON® 25(OH)D</td>
</tr>
<tr>
<td>2</td>
<td>Quest Diagnostics</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
<tr>
<td>3</td>
<td>U. Western Australia</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
<tr>
<td>4</td>
<td>Covance Central Lab. Services, Inc.</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
<tr>
<td>5</td>
<td>LabCorp</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
<tr>
<td>6</td>
<td>U of Leige, Belgium</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
<tr>
<td>7</td>
<td>Mayo Clinic</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
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<tr>
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<td>----------------------------</td>
</tr>
<tr>
<td>8</td>
<td>Siemens</td>
<td>Chemiluminescence Immunoassay</td>
<td>ADVIA Centaur®</td>
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<tr>
<td>9</td>
<td>Path Assoc Med Lab, LLC</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
<tr>
<td>10</td>
<td>IDS</td>
<td>Immunoassay</td>
<td>IDS-iSYS</td>
</tr>
<tr>
<td>11</td>
<td>IDS</td>
<td>Immunoassay</td>
<td>25(OH)D EIA</td>
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<tr>
<td>12</td>
<td>UCC</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
<tr>
<td>13</td>
<td>Douglas Hanly Moir Pathology</td>
<td>LC-MS/MS</td>
<td>Total 25(OH)D</td>
</tr>
</tbody>
</table>
Mean Deviation (%Bias) of 25-OHD assays from the NIST Reference Measurement Procedure: DEQAS Last Two Distribution Cycles
Finally, Ask Yourself?

- What’s your assay’s CV? Is it ≤ 10%?
- What’s your assay’s mean Bias? Is it ≤ 5%?

More importantly, what is the proportion of Bias estimates between ± 5%?
- Proportion between ±5% is the index of standardization progress from PT/EQA.
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Thank you!

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Join the VDSP effort!

http://ods.od.nih.gov/VitaminD
Sign up for the VDSP e-mail list!

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