



Take Two: Gearing Up for the Next Vitamin D Commutability Study

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As intense interest in vitamin D has boosted demand for testing, many labs have developed their own methods, even as manufacturers introduce new immunoassays for this growing market. However, vitamin D standardization is not complete and some assays can still disagree, potentially confusing clinicians and limiting the utility of these assays for patient care. Since 2010, the Vitamin D Standardization Program (VDSP), part of the National Institutes of Health Office of Dietary Supplements (ODS), and other stakeholders have made significant strides in promoting the standardization of total 25-hydroxyvitamin D [25(OH)D] in order to improve clinical decision-making and inform clinical and public health practice (3,4).

However, critical work remains before laboratories, clinicians, and

patients can have full confidence that 25(OH)D measurements will be comparable over time, location, and laboratory procedure on an international scale. Now, VDSP and its partners are launching a study that aims to ensure the performance of reference materials by demonstrating commutability. Commutability means that reference materials behave like patient samples when tested in a clinical or research laboratory using a specific laboratory's procedure. As such, gauging commutability requires examining as many commercially available laboratory procedures and laboratory-developed procedures as possible. This article describes the new VDSP Commutability 2 Study and explains how assay manufacturers and individual laboratories can participate.

Study Design

VDSP and international collaborators already have developed the essential building blocks of standardization: reference measurement procedures (RMPs) and standard reference materials (SRMs) that together set a

gold standard for aligning the results of different assays and methods. Developed by the National Institute of Standards and Technology (NIST) and Ghent University, the RMPs have improved the standardization for assay calibration, and are approved by the Joint Committee for Traceability in Laboratory Medicine (JCTLM).

Similarly, the groundwork for implementing these standards has been laid by the Centers for Disease Control and Prevention's (CDC) Vitamin D Standardization Certification Program (VDSCP); the College of American Pathologists (CAP) Accuracy-Based Vitamin D Survey (ABVD Survey); and the Vitamin D External Quality Assessment Scheme (DEQAS) (4). NIST's SRMs are used as trueness controls, and the CAP and DEQAS PT/EQA programs establish and monitor an individual clinical or research laboratory's traceability to the NIST and Ghent RMPs.

NIST and the National Institutes of Health Office of Dietary Supplements, in collaboration with CAP and DEQAS, are coordinating this international study to test the commutability of NIST vitamin D SRMs and CAP/DEQAS test materials. VDSP also has worked closely with AACC and with the International Federation of Clinical Chemistry and Laboratory Medicine on the design of the study.

The overall design of VDSP Commutability 2 follows the Clinical and Laboratory Standards Institute (CLSI) guidelines EP14-A3 and EP30-A (5,6). The sample sets will consist of 50 healthy donor samples with native total 25(OH)D levels ranging from 5 nmol/L to 150 nmol/L (2 ng/mL to 60 ng/mL), as well as the serum-based NIST SRMs which have been value-assigned for 25(OH)D. In addition, PT/EQA materials from DEQAS and CAP will be included. The donor samples will be collected and prepared by Solomon Park Research Laboratories according to CLSI C37-A guidelines (7).

Donor sample sets will be blinded to participants. NIST SRMs in this study will include SRM 972a Vitamin D Metabolites in Frozen Human Serum (4 levels of material) and SRM 2973 Vitamin D Metabolites in Frozen Human Serum

(High Level, one level of material). In addition, a yet undetermined number of DEQAS and CAP samples are expected to be included in the test materials.

VDSP will provide participants with a run order protocol that will require the analysis in duplicate on a single day of all donor and test samples. This is intended to minimize the effects that may confound commutability assessment, such as lot-to-lot variability of calibrators and reagents. Target values for samples will be assigned by the NIST ID-LC-MS/MS RMP (8). While commutability will be based on the total 25(OH)D value, additional vitamin D metabolites such as 3-epi-25(OH)D3 and 24,25(OH)₂D3 will also likely be value-assigned by NIST ID-LC-MS/MS methods to investigate correlation with any trends seen in the data. Statistical assessment of the data will be conducted based on CLSI EP14-A3 and EP30-A guidelines (See Figure). To assess commutability under normal measurement conditions, only the first result from clinical laboratories will be considered, similar to typical patient sample analysis.

During the participant recruitment phase, VDSP will distribute to interested parties a questionnaire on assay and platform system, assay performance data (% coefficient of variation [CV]), as well as verification that laboratories agree to be identified in eventual summary publications. The utility of a previous VDSP commutability study was limited by how few laboratories agreed to publish their data.

Benefits for Participants

VDSP Commutability 2 Study is being designed to benefit all parties involved. All participants—including manufacturers, clinical, and research laboratories—will have access to a set of 50 single donor serum samples free-of-charge and will contribute directly to an international effort to standardize vitamin D measurements. VDSP will provide participants with a final report listing the NIST target values for all donor serum samples as well as the SRM and PT/EQA test materials. Reports will also include an evaluation of commutability and intra-batch bias versus NIST target values.

First and foremost, the agencies and programs providing study test samples, including NIST, CAP, and DEQAS, will better understand the commutability of their current SRMs and PT/EQA materials with a variety of different measurement assays and platforms. With this knowledge, the stakeholders in this partnership will work to improve current materials and provide information on existing gaps in metabolite concentration ranges. Such improvement in SRM and PT/EQA tools promotes the standardized measurement of total 25(OH)D worldwide by clinical and research laboratories.

Finally, for assay manufacturers, the results of this study will provide valuable data needed to recommend SRMs and PT/EQA programs to their customers. Results for particular samples may alert manufacturers—or those who are evaluating their in-house developed assays—to gaps in assay performance, such as identifying unanticipated cross-reactive molecules.

How to Get Involved

The focus of the study will be on commercially available assay platforms, and the goal is for all manufacturers to participate. Assays that are in development at the time of the study will also be considered. In addition, we welcome the participation of clinical and research laboratories using commercially available assay platforms, national or subnational nutrition surveys regardless of assay platform, and clinical/research laboratories with in-house developed assays. All laboratories wishing to participate must meet the minimum VDSP performance guideline of $CV \leq 10\%$. An additional requirement is that participating laboratories must agree prior to the study that their results—including the identification of assay platform and the laboratory of analysis—will be included, as appropriate, in papers published about the study. The number of participants will be limited; selected by NIST and ODS to balance coverage of the different assays and regions of the world.

For more information about the study and to let us know if you are interested in participating, please contact us at: vdsp@mail.nih.gov.

We look forward to working with you on this important commutability study. ■

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FOR MORE INFORMATION ABOUT THE STUDY AND TO LET US KNOW IF YOU ARE INTERESTED IN PARTICIPATING, PLEASE CONTACT US AT:

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