Original Article

Standards and Measurements for Assessing Bone Health—Workshop Report Co-Sponsored by the International Society for Clinical Densitometry (ISCD) and the National Institute of Standards and Technology (NIST)

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Abstract

This article reports and discusses the results of the recent ISCD–NIST Workshop on Standards and Measurements for Assessing Bone Health. The purpose of the workshop was to assess the status of efforts to standardize and compare results from dual-energy X-ray absorptiometry (DXA) scans, and then to identify and prioritize ongoing measurement and standards needs.

Key Words: Bone mineral density; calibration phantoms; edge detection; International Society for Clinical Densitometry (ISCD); National Institute of Standards and Technology (NIST); reference data; region of interest; standards.

Introduction and Motivation

Bone mineral density (BMD) has long been one of the primary tools used to evaluate bone health and predict fracture risk. The status of BMD values as measured by dual-energy X-ray absorptiometry (DXA) devices was elevated further

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as a result of the 1994 World Health Organization (WHO) report in which osteoporosis was effectively defined with respect to a T-score, a dimensionless and statistically based surrogate for BMD. Despite its history and widespread use, accurate measurement of BMD remains a problem. The Surgeon General's 2004 report cites variability as a central limitation in BMD measurements *(1)*:

"One important concern about the interpretation of results is the variability that exists across different types of BMD machines (even those made by the same manufacturer), and across similar types of machines made by different manufacturers. Bone mineral density measured on one type of machine cannot be accurately compared with BMD measured on a different type of machine, nor can BMD performed on the same type of machine at two different locations. There is also variability in the ability of technologists to perform the tests, in the training and ongoing certification of technologists, and in interpretations of results by physicians, each of which can undermine the comparability of results. As a result of all of these factors,

daily equipment checks and a quality control system related to both the methodology and reporting of test results is critical to ensure the validity of DXA analysis…''

Improvements in the accuracy of DXA systems would have a positive impact on the field of bone health and would reduce social and economic costs significantly. New treatments could emerge as drug benefits, currently not discernable due to measurement uncertainties, become apparent. Similarly, present longitudinal studies may be plagued by measurement drift, thereby compromising results from large clinical trials. Existing variabilities in BMD measurements, and how to best address them, motivated the International Society for Clinical Densitometry (ISCD) and the National Institute of Standards and Technology (NIST) to explore areas of mutual interest.

Doctor Paul Miller founded the ISCD in 1993 to advance excellence in assessing skeletal health. Under his leadership, a small group of physicians gathered in June 1992 at the Wyndham Hamilton Hotel, Itasca, Illinois, to discuss problems associated with the practice of clinical densitometry in the United States. They represented the medical disciplines of endocrinology, internal medicine, nephrology, and rheumatology. Today, the ISCD advances excellence in the assessment of skeletal health by promoting a broader understanding of bone mass measurement technologies for clinical applications. For additional background, the following websites describe the ISCD's mission, Official Positions, and its many programs *(2)*:

- ISCD mission statement
  http://www.iscd.org/Visitors/about/mission_statement.cfm
- ISCD Official Positions for 2005
  http://www.iscd.org/Visitors/positions/ISCDPositions SlideShow2006-02-08forWEB.pps#14

As the United States (US) government's National Measurement Institute, the NIST assists stakeholders in a vast array of industry sectors with measurement and standards needs. The goal of the NIST's involvement is to enhance efficiency and productivity, and to increase the rate of technological innovation. The NIST is not a regulatory agency, but rather serves as a neutral third party, providing technical input in matters related to measurements, standards, and assessments of interoperability to a variety of customers (i.e., standards committees, regulatory agencies, and the private sector where appropriate). The NIST has provided standards and measurements for health care since the 1930s *(3)*. For example, the NIST develops, maintains, and disseminates the national measurement standards for radioactivity for nuclear medicine and ionizing radiation for diagnostics and radiation therapy through calibrations and standard reference materials. This includes the dosimetry standards for radiation therapy, brachytherapy *(4,5)*, and diagnostic X-ray beam sources. As a result of the Mammography Quality Standards Act of 1992, which required the Food and Drug Administration to set up a certification and inspection program for US mammography clinics, operators and inspectors of more than

13,640 US mammography centers now trace the accuracy of their X-ray exposure measurements to the primary X-ray standards maintained by the NIST *(6,7)*. These standardization efforts have resulted in significant improvements in mammography, including better-characterized X-ray systems with well-defined X-ray beam quality parameters, such as kilovoltage and half-value layers; cross-comparability of mammograms scanned at different clinics and on different equipment; and improved diagnostic accuracy, credibility, and patient care *(8)*. The following websites describe some of the NIST's current programs in areas of possible interest to the clinical densitometry community:

- X-ray interactions and materials properties databases: http://www.nist.gov/srd/index.htm
- Clinical reference standards related to ionizing radiation: http://physics.nist.gov/Divisions/Div846/div846.html

In contrast, DXA technologies used to assess bone health presently lack absolute and rigorous traceability to the international system of units, the foundation for comparability of measurements throughout industry and the world. Hence, BMD measurement values from different manufacturers can differ in absolute terms by 12% to 18% *(9)*. The clinical densitometry community has recognized these issues and has initiated standardization efforts. These include the use of T-scores and Z-scores, standardized BMD (sBMD) *(10,11)*, and the development of a national quality assurance program for bone health. As we will discuss below, the clinical densitometry community would benefit from additional support to facilitate these initial, positive steps.

With the previously mentioned issues in mind, the ISCD and NIST co-sponsored a one-day Workshop on Standards and Measurements for Assessing Bone Health at the 12th Annual Meeting of the International Society for Clinical Densitometry (ISCD) in San Diego, California on February 4, 2006. This workshop was an information-gathering forum and part of the NIST's strategic assessment of the US measurement system. The objectives of the workshop were to:

- Discuss measurement needs and sources of variability in BMD and T-scores.
- Identify systemic gaps and weaknesses in existing standards and supporting data for technologies used to assess bone health.
- Establish priorities for addressing the identified measurement and standards needs.

More than 55 physicians, clinicians, reference data experts, and manufacturers of bone imaging equipment attended the all-day workshop. The morning session included an overview of the NIST by Dr. Herbert Bennett and presentations from invited speakers Drs. Nelson Watts, Thomas Hangartner, Anne Looker, Paul Miller, and Didier Hans. They identified standards and measurement needs for bone imaging methods in central and peripheral densitometry, compared standard reference databases, and summarized quality control programs in densitometry around the world. They also addressed

barriers to the reduction of DXA variability and to the widespread implementation of quality assurance and quality control (QA and QC) protocols, as well as potential solutions for overcoming these barriers. The afternoon session consisted of a panel of experts, Drs. John Shepherd, Steven Petak, and Lawrence Hudson, who represented industry, ISCD, and NIST, respectively. The manufacturers of DXA equipment do not have a trade organization to represent their common perspective and needs for calibration standards, reference data, software validation, and imaging formats. Thus, in many ways, the ISCD's Committee on Standards of Bone Measurement, of which Dr. Shepherd is the chairman, serves as a surrogate forum for the DXA industry. The panelists and audience discussed the measurement needs identified during the morning session. At the conclusion of the workshop, the attendees prioritized the identified standards and measurement needs to reach a tentative consensus on the most significant ones. More details of the workshop, as well as slides used by the speakers, can be found at http://usms.nist.gov/workshops/BoneHealth.htm.

We report here on the preliminary findings and discussions resulting from this workshop. In the first section that follows, we summarize in broad terms the principal measurements and data that are used in the course of a DXA determination of BMD and T-score. The intention is to define, as concretely as possible, the sources of variability in these values. In the second section, we discuss past and present attempts to standardize these measurement processes. In the third section, we present the preliminary list of needs that emerged from the participants following a panel discussion of the issues and possible solutions to those needs identified by the speakers and audience. We conclude with future prospects for addressing the most urgent needs.

DXA Measurements and Sources of Variability

The three main sources of inaccuracy and imprecision in DXA scans are the equipment, the technologist, and the patient. In this section, we emphasize the technical limitations of DXA equipment and reference databases. In the last section, we mention the requirements for improved training and skills of the technologist. We do not discuss in this article the inhomogeneity of soft tissue composition within the patient and its variation with time. However, they are very important to keep in mind, because even after all the technology improvements and innovations have occurred, the soft-tissue inhomogeneity and its time variation are fundamental limitations to the DXA measurement process for BMD and determine how well the DXA technology ultimately performs.

There are three manufacturers of central DXA systems in the US: Hologic, GE Lunar, and Cooper Norland. Each manufacturer offers a variety of models. Many reports within the bone health community show that different DXA devices, both within and across manufacturers, return different BMD values. Generally, these BMD values correlate well with

one another and are repeatable, yet they exhibit systematic discrepancies. The lack of cross-comparability is a core issue in the field of densitometry and was referenced by nearly all speakers in the morning session. Doctor Nelson Watts spoke of one study in which it was observed that a very large percentage of DXA devices returned BMD values to within 1% of the error reported by the manufacturer *(12)*, yet the variation across manufacturers differed from top to bottom by as much as 10% of the mean value *(13)*. In his talk on calibration phantoms, Dr. Thomas Hangartner emphasized the distinction between precision and absolute accuracy, and variability in the latter of the order of 10%.

Each DXA device contains internal hardware and software components that are proprietary and that should provide the technological basis for competition and innovation among manufacturers. Unfortunately, the present lack of cross-manufacturer standardization restrains competition by limiting physician choice in the market place and by restricting where patients can go for follow-up DXA scans. The DXA devices, which are designed to measure the same quantities—BMD, bone area, bone mineral content (BMC), T-score, and Z-score—should agree with each other to within acceptable tolerances required for accurate diagnosis and patient monitoring during the course of treatment. Some believe that current DXA devices do not meet acceptable cross-manufacturer interoperability tolerances for many treatment protocols.

In the context of improving comparability and accuracy, the workshop presentations and discussions taken as a whole highlighted three areas in which measurement steps are of a fundamental importance in the path from a bone scan to an inferred BMD and T-score: hardware, software, and reference databases. We hope is that our delineation of these steps will help provide a framework for improvements in the accuracy, comparability, and clinical utility of DXA devices.

DXA Hardware: Beam Energies, Geometries, and BMD

The reported BMD given by a DXA scan is the mean value of pixel-by-pixel measurements of the bone mass density within a defined area that is called the region of interest (ROI). Thus, the primary DXA scan parameters are BMD and area. The measurement of BMD is highly dependent on the hardware characteristics specific for each device. Differences within the DXA system hardware include: x-ray generation, choice of energy levels, beam and detector geometries, and analysis methods. The time stability of some of the more sensitive internal components contributes to variability. Like any other power generating system, x-ray generating devices may change over time, and presently the user community does not know the extent to which device manufacturers control or monitor this drift. Another source of variability is the method or the extent to which manufacturers mitigate inherent inaccuracy due to the two-component assumption in the DXA method *(14)*.

DXA Software: Regions of Interest (ROI), Edge Detection, and Bone Area

The X-ray generation, detection, and analysis issues previously discussed result in variability of the BMD of a patient. An edge detection algorithm, implemented in software, is applied to the pixel-by-pixel bone mineral density map to find the bone outline and to measure the projected area. The BMC is a derived quantity obtained by multiplying BMD by area of the ROI. As BMC is not often used by the clinical community, the variability and accuracy of BMC are not well-quantified. Computation of this area relies heavily on the selection of a region of interest (ROI) and image analysis software, and is an independent source of variability of BMD values.

The selection of the ROI is fundamentally important in computing area, and it defines the portion of the patient's bone that is relevant for evaluation of bone mass density and area. The differences in the anatomical region being scanned (ROI)—"central" versus "peripheral" DXA rely substantially on the degree of standardization that exists within the DXA community. For example, nearly all DXA scans of the spine analyze the lower lumbar vertebrae L1–L4 as the default ROI, and return BMD computations of each as well as various averages *(15)*. There is slightly less agreement on the definition of the ROI in the analysis of hip DXA scans. Even though analysis of the total hip has been an option, most manufacturers of central devices recommend analyzing sub-areas of the hip defined with respect to discernable characteristics of the patient's hip geometry. Dr. Paul Miller showed in his presentation that the lack of standardization of the selection of the ROI is perhaps greatest in peripheral DXA technologies and may be viewed as a significant contributor to cross-manufacturer variability for these noncentral scans *(16)*.

Defining the ROI is only part of the task of determining bone area. Proprietary edge-detection software is used to determine the boundaries within the X-ray image that separate bone from soft tissue within the ROI. In addition to user intervention, there are several free parameters in edge-detection algorithms such as pixel value thresholds, averaging schemes to reduce high-bandwidth spatial noise, and deblurring schemes to enhance focus. Any of these software variables can have substantial impact on the definition of the bone/soft-tissue boundary. In turn, this boundary definition directly affects computed bone area and the reported BMD value.

We treat these software issues as sources of variability that are independent from the hardware considerations, such as beam geometry and energy, as previously discussed. This may be an oversimplification because deblurring and averaging algorithms can be optimized when models for the sources of image blur and noise are available. Such models would inherently depend on the hardware used to acquire the image. However, presently, we do not know whether DXA manufacturers have incorporated this type of optimization into their image analysis software. If the manufacturers have not, then it would be possible, in principal, to require that all DXA devices output in a standardized format a pixel-by-pixel report of the BMD as determined by the hardware. It would then be relatively easy for users to input this "image" into the analysis software of any of the DXA manufacturers, or even third-party software for that matter, and perform the subsequent ROI selection and area measurement.

DXA Reference Data: Normative Databases and the T-Score

The BMD values from DXA scanners and proper statistical references are central to a given patient's diagnosis and treatment. The diagnosis of densitometric osteoporosis is currently based on the T-score. The T-score is defined as the difference between the patient's BMD value and the mean BMD value of a young reference population divided by the standard deviation in BMD values for the same defined reference population. The T-score approach was originally developed by the WHO for use in epidemiological studies of hip data. As such, it presents a number of problems. One of these problems arises from the need to compare patient data with a reference population, because absolute BMD values generated by DXA systems from different manufacturers vary. Unless a study has been performed to generate an algorithm to provide equivalent BMD values from different DXA systems, each manufacturer requires its own reference dataset, which in turn may lead to discrepant diagnoses caused by differences in the reference databases being used. The BMD varies by gender, race and ethnicity, and skeletal site. Therefore, a single standard reference database that is not specified for gender, ethnic, and skeletal-site may not be valid. Standard reference data are now available for the hip and will soon be available for the lumbar spine and whole body for a representative sample of men and women from various ethnic groups and races who were included in the National Health and Nutrition Examination Survey (NHANES). The NHANES started measuring lumbar spine in 2005. Another problem for use in diagnosis includes uncertainties about application to men, nonwhite women, and children, and to skeletal sites other than the hip and spine. Different skeletal sites have different peak bone masses and lose bone at different rates. Also, as noted in Dr. Watts' presentation, there are differences in mean values of femoral BMD between phase 1 and phase 2 of the NHANES III for the hip *(17)*.

Standardization Efforts

We summarize past and present standardization efforts in support of improving the clinical practice of diagnosis and treatment of bone disease as discussed by the workshop speakers.

Calibration Phantoms

Doctor Thomas Hangartner addressed the nonexistence of standard, fully-characterized DXA phantoms as a barrier to

resolution of inconsistent BMD measurements from different machines and from upgrades of the same machine. As previously outlined, both X-ray extinction and image analysis are fundamental in determining the accuracy of BMD values from DXA scanners. Numerous DXA phantoms exist. Nevertheless, problems remain in that they: are used without a common reference standard and protocol, may possess poorly characterized X-ray extinction properties, and may use nonstandard geometric morphologies. Phantom standardization may serve to gauge the accuracy of both BMD and area measurements. Recognition that these are distinct operations entails the possibility that the optimal phantom solution could in fact be a suite of artifacts, each designed to gauge the different measurements performed by DXA devices.

Standardized BMD

Since the 1990s, the Committee on Standards of Bone Measurement (CSBM) of the ISCD, which was formerly the independent International Committee of Standards in Bone Measurement (ICSBM), has commissioned various studies for the standardization of spine *(18)*, hip *(19)*, and forearm *(20)* BMD as measured by DXA. As part of these studies, medical researchers at the University of California, San Francisco (UCSF) initiated the development of "standardized BMD" (sBMD). Recognizing the high correlation but systematic inconsistencies in BMD values measured on the same patient using scanners supplied by three major manufacturers, they performed a series of studies and a controlled regression analysis. The result was a set of linear, derived equations for re-scaling measured BMD values from any of the existing scanners to a common quantity referred to as sBMD *(18)*. These equations now serve as a way to combine and compare data from different manufacturers. Subsequent studies refined the analysis and extended it to other scan sites *(21)*. Nevertheless, despite the desirable effect of removing cross-manufacturer incompatibilities, sBMD is not widely used in clinical practice.

The ISCD CSBM recently investigated several topics concerning cross-calibration and technical aspects of bone densitometry. A report with recommendations was presented to the Expert Panel at the ISCD 2005 Position Development Conference. The ISCD Official Positions on these topics, resulting from that conference, with the supportive evidence and justification for these positions, were published *(22)*.

Reference Data

Doctor Anne Looker presented the current state of reference databases relevant to bone health. Presently, the hip is the only skeletal site with standard reference data from the NHANES III; it is now used by all manufacturers as the standard reference data for calculating the T-score *(23)*. The expense and competition for time in a general health survey may preclude using NHANES to obtain data for a large number of additional skeletal sites. Obtaining a representative sample of other races and ethnic groups in NHANES would require a significant increase in the overall survey sample and thus is very unlikely. As brought up in subsequent discussions, an alternative to obtaining data for groups and other skeletal sites not covered by the NHANES may be to conduct community-based studies that use a standardized protocol to select the sample and perform the measurements. However, the success and validity of such decentralized studies would seem at the very least to be contingent on increasing the accuracy of individual BMD measurements and ensuring that they are consistent across scanning centers and devices.

Global Quality Control and Assurance Programs for DXA

Improvements in measurement accuracy and refinements in reference data could easily be undermined by poor implementation at the clinical level. Doctor Didier Hans discussed the state of quality control and assurance measures that are being implemented outside the US. The French government passed a law in April 2005 that mandates compliance, beginning in June 2006, with its DXA quality control procedures, for reimbursement. The DXA measurements for compliance must be demonstrated in the presence of a French government inspector. This new French law has great implications for US manufacturers who dominate the global DXA scanner market. The US, too, could greatly benefit from a National Quality Assurance (QA) and Control (QC) Program. Before nonexperts impose a QA and QC program for the US, however, clinicians and other stakeholders in bone health should define the best QA and QC program that is based on scientific evidence and that considers the routine clinical load.

Future Efforts

Possible Solutions

The attendees proposed several solutions for each of the measurement problems and standardization challenges outlined in the previous sections on DXA Measurements and Sources of Variability and Standardization Efforts. We list them here in no particular order of priority, and we categorize them with respect to the subheadings in their respective sections.

Suggestions concerning the DXA hardware and the determination of bone mass included:

- Measuring the impact of scanner drift, variation in X-ray source intensity, and other hardware parameters.
- Validating that correct BMD values are obtained over a physiologic range of bone thicknesses and body mass indices.

Suggestions concerning ROI and image analysis included:

- Agreeing on standard ROIs to evaluate specific anatomical sites of bone loss. Cooperation is necessary among all manufacturers.
- Advanced research is needed to assess various edge detection approaches to determine the sensitivity to bone size, BMD, scanner drift, and its self-correction.

- Creating a standardized image format and calibration so that all devices would produce a digital image with an identical relationship between pixel value and mineral mass that is independent of the DXA scanner's manufacturer.

Suggestions concerning increasing and improving the reference databases included:

- Surveying race and ethnic groups which are not currently covered in the NHANES.
- Using these databases in clinical settings while concurrently developing and integrating software for both new and existing DXA systems.

Suggestions concerning standardization efforts included:

- Developing and deploying accurate phantom technologies that manufacturers can use for performance validation of DXA systems.
- Developing and deploying quality assurance protocols that define best practices for DXA scanner calibrations and that are based on quantitative performance metrics provided by well-characterized phantom technologies.
- Creating standardized BMD (sBMD) values across different DXA manufacturers for other skeletal sites in addition to the hip and spine.

Needs Prioritization

During the afternoon session, attendees discussed and voted on the relative priority rankings for the following DXA needs. Because some of the needs listed below overlap with one another and because not all stakeholders were present, the following list and priority ranking should be viewed as preliminary. Success in meeting the top two needs of the ISCD community, which are major components of the ISCD mission, requires success in meeting most of the remaining needs that are listed in priority order as determined by those attending the afternoon session.

Training and Performance:

1. Mandatory training and technologist validation
2. Mandatory technical performance standards for all densitometry clinics

Measurements and Standards:

3. A phantom or set of phantoms that validate accuracy at all regions of interest (ROIs)
4. National clinical equivalence across manufacturers
5. Standardization of ROI
6. More complete and common reference data
7. Government endorsement of precision measurements (i.e., global Institutional Review Board approvals for precision studies)
8. Standardized report formats that enable comparisons of reports regardless of manufacturer or models of DXA scanners

9. Define response to drifts or shifts in calibrations
10. A reference accuracy standard that defines g/cm^2 and g/cm^3
11. Standardized units of BMD, BMC, and area
12. Standardization of edge-finding algorithms and their performance with respect to different soft-tissue and density conditions
13. Standardization, ROIs, reference data, and the like for peripheral densitometers

WHO Fracture Risk Model

The WHO has a major effort underway to improve diagnosis of osteoporosis by creating an absolute fracture-risk model. Although details of the model are under development, the intent is to incorporate several clinical variables in combination with a carefully developed model so as to estimate a risk for osteoporotic fracture over a given time interval. Input variables presumably would include BMD or Z-scores, as well as several other variables such as current age, sex, prior fractures, body mass index, use of corticosteroids, secondary osteoporosis, parental history, and alcohol and tobacco use that are determined to contribute to overall fracture risk, independent of BMD measurements. The unique contribution made by BMD to the overall assessment of fracture risk is through the Z-score. This effort has ramifications for allocating resources in terms of research time and money. The primary diagnostic criteria for assessment of osteoporosis is a T-score ≤ 2.5 standard deviations below young normals. This fixed BMD threshold (T-score ≤ -2.5) is univariate, and its statistical surrogate (ie, the T-score) is the sole quantity of interest. Therefore, presently, the variability in BMD has a direct impact on both diagnosis and, to a large extent, treatment. A multivariate fracture-risk model would balance BMD inconsistency with the variability of other independent quantities.

Roles for NIST

The attendees also suggested several roles for NIST. The ones following possible are not listed in priority order:

- Facilitate cooperation among manufacturers and research groups, especially in the development of one phantom for cross-calibrations.
- Work with all stakeholders to standardize techniques for measuring parameters that correlate with bone health and strength. In addition to BMD, bone area, BMC, and T-scores previously discussed, these include developing technologies to measure ultrasonic attenuation coefficients in bone, stiffness index for quantitative ultrasonic scans, and speed of sound in bone, bone marrow, and soft tissue surrounding bone.
- Enable the use of absolute units (BMC [expressed in gm] and bone area [expressed in cm^2]) that are traceable to the international system of units for mass and area.
- Facilitate the development of standards for reports from DXA scanners.

- Coordinate with other groups, such as the ISCD, QA and QC efforts to unify standards across national boundaries. The ISCD is developing a Bone Densitometry Facility Accreditation Program that will address quality issues by defining standards of performance and operation *(24)*.

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