



No Limits

Annelee Spano Lander of CoreLab Partners and Reta C Rupich, an independent consultant, look back over 50 years of the journey of DEXA and consider how it will evolve in the future

In 1963, John Cameron and James Sorenson introduced single photon absorptiometry (SPA) to measure peripheral bone mineral density (1). Soon after, the first commercial SPA instrument was produced by Norland Corporation, followed by Lunar Radiation Corporation (now GELunar) and several others. With this technology, the wrist was submerged or embedded in water to simulate soft tissue, a ^{125}I energy source was used and a single one centimetre long scan was made across the forearm (2).

In 1965 came the addition of a dual energy source for measuring regions of interest that could not be easily submerged in or surrounded by water. However, dual photon absorptiometry (DPA) was not employed until the 1980s when clinical applications became relevant. Gadolinium (^{153}Gd), which emits two distinct energies, became available in the 1970s and was used in the first commercially introduced DPA units. At that time, Lunar made DPA commercially available for the measurement of spine and hip bone mineral density (BMD), along with total body composition (bone mineral, fat and fat-free mass) (3).

DEXA TECHNOLOGY

Resolution limits, degrading energy source and long scan times (20 to 40 minutes) led to the transition from DPA – with its ^{153}Gd source – to dual energy x-ray absorptiometry (4). Hologic Inc introduced them in 1987 and it is common to see the machines with this energy source abbreviated as either DEXA or DXA. The use of the x-rays as an energy source increased resolution, precision and decreased the scan time to six minutes (5). Later improvements included replacing rectilinear scanning with array or fan beam which further reduced scan times to one to two minutes.

A bone loss of at least 40 per cent is necessary for it to be detected visibly by a radiologist in a standard x-ray (6). In addition, a patient is exposed to approximately $1.5\mu\text{Sv}$ of radiation, which is just over one third of the radiation the average person in the US is exposed to annually from naturally occurring sources (7). With DEXA technology there is a one to two per cent precision *in vitro* and a two to four per cent precision *in vivo* (8). The effective radiation dose to a patient from a DEXA scan is $0.001\mu\text{Sv}$ (7). The low radiation dose and high precision of DEXA instruments made them the preferred method of measuring bone density. The tool was, and still is, commonly utilised in the assessment of patients with skeletal

disorders, patients requiring treatment that adversely affect bone health, as well as those with issues of obesity and/or fat distribution.

METHOD OF CHOICE

High precision and accuracy, along with the low radiation dose and low cost, made DEXA the method of choice for longitudinal monitoring of bone mineral density in clinical practice and for pharmaceutical clinical trials. Draft guidelines for developing osteoporosis drugs were initially issued by the FDA in the 1980s and last issued in 1994 (9). The guidelines include recommendations for performing

Figure 1: Sample DEXA – bone densitometry scan of left femur

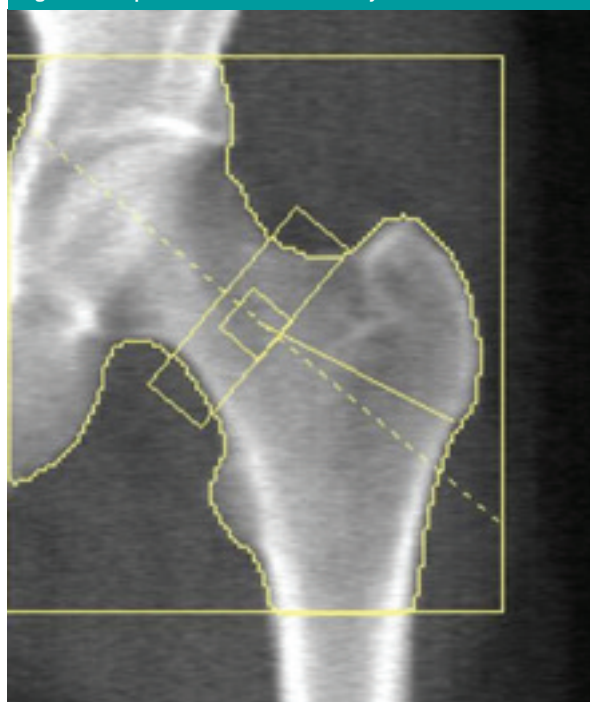


Figure 2: Sample DEXA – dual energy x-ray absorptiometry of the lumbar spine

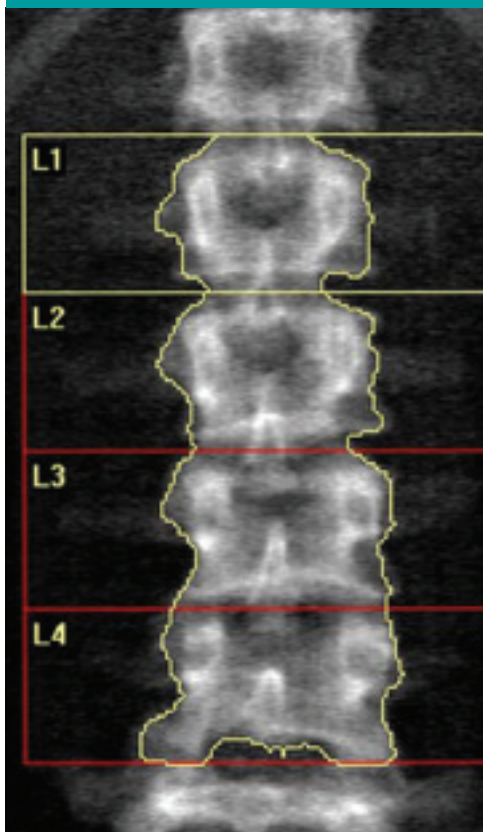
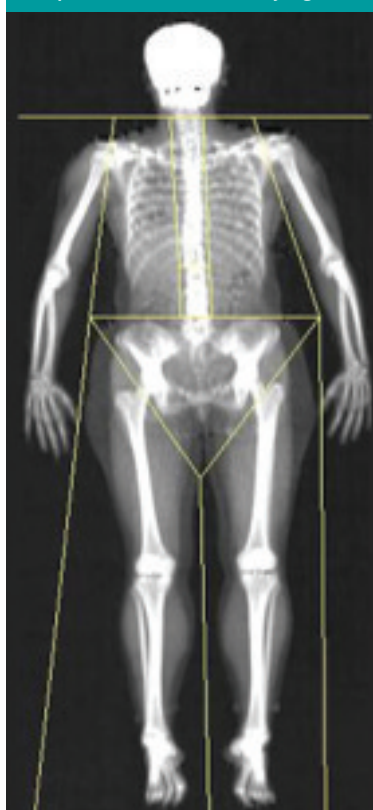


Figure 3: Sample DEXA – whole body composition scan image. The lines are used to separate and measure the body regions



shipment of the gold standard phantoms are tracked to ensure all participating sites receive them, the scans are centrally analysed and the results are statistically analysed to assess calibration differences. The implementation of all of these measures has now resulted in the approval, execution and acceptance of final data for hundreds of protocols for all phases of clinical trials in many therapeutic areas.

DEXA DEVELOPMENTS

There have been constant refinements of the DEXA tool to better measure and extend the skeletal assessment and expand the DEXA instrument capabilities. Since the time Cameron first introduced the idea of using small amounts of radiation to measure bone mass, instruments have continued to evolve. As mentioned above,

cross-calibration of DEXA scanners using the same phantom across sites, along with longitudinal tracking of each individual instrument's performance throughout the clinical trial. One of the first commercial DEXA quality assurance (QA) centres was formed in response to a request made by Merck & Co who were conducting a large multi-centre osteoporosis trial, using Hologic instruments. They requested Hologic provide QA services, and as a result Hologic created a medical data management (MDM) division specifically for this purpose.

Hologic's MDM implemented QA processing which reduced variation in patient scan results by centrally analysing scans and validated BMD results through monitoring DEXA instrument performance over the course of the study. Besides these key components of central image analysis and instrument quality control (IQC), an additional component is the increased collection of QC phantom data and analysis across sites (cross-calibration). The QA centres evaluate phantom scan results for subtle changes in density, and flag results that show patterns indicative of calibration shifts and/or drifts. Quality control algorithms were implemented to allow the QA centres to provide correction factors for patient data obtained during a period of higher than acceptable flux or less than expected variation on one side of the running average.

To reduce the cost and time needed for cross-calibration, QA centres worked with couriers and sites to provide the necessary paperwork and schedule to enable the phantom to be shipped from site to site, as opposed to being carried by hand. The

scans now take much less time and are much more precise. In addition, more recent developments include hip structural analysis (HSA), which uses cross sections of the 2D scan image of the proximal femur to algorithmically calculate bone strength. Instruments with the fan beam technology can accurately perform vertebral fracture assessment (VFA) of thoracic and lumbar vertebrae. Other ongoing DEXA developments include the improvement of reference ranges, especially in the paediatric population, where comparing clinical results to normal growth is critical. The Frax tool integration is another addition to some DEXA devices, which offers a system to predict risk from DEXA readings to facilitate decisions for treatment plans (10).

CONCLUSION

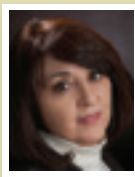
The DEXA device for the measurement of bone densitometry which was largely ignored when it was invented almost 50 years ago, has continued to evolve. By increasing the uses and capabilities of the DEXA instrument, the manufacturers are ensuring that the reliability, uses and market for DEXA measurements will continue to grow both for patient care and within clinical trials. As DEXA capabilities expand, so do the responsibility of QA centres to develop and implement valid quality control procedures to ensure meaningful results from clinical trials.

References

1. Cameron JR and Sorenson J, Measurement of bone mineral *in vivo*: an improved method, *Science* 143: p230, 1963

2. Cameron JR, Mazess RB and Sorenson JA, Precision and accuracy of bone mineral determination by direct photon absorptiometry, *Invest Radiol* 3: p141, 1968
3. Mazess RB, Pepler WW, Harrison JE *et al*, Total body bone mineral and lean body mass by dual photon absorptiometry, *Calcif Tissue Int* 33: p365, 1981
4. Roos B, Dual photon absorptiometry in lumbar vertebrae: Theory and method, *Acta Radiol Ther Phys* 13: p291, 1974
5. Wahner HW, Dunn WL, Brown ML *et al*, Comparison of dual energy x-ray absorptiometry and dual photon absorptiometry for bone mineral measurements of the lumbar spine, *Mayo Clinic Proc* 63: pp1,075-1,084, 1988
6. Harris WH and Heaney RP, Skeletal renewal and metabolic bone disease, *N Engl J Med* 280(4): pp193-202, 23 January 1969
7. RSNA & ACR published Radiation Exposure in X-ray and CT Examinations, *Safety in Medical Imaging Procedures*, 2008
8. Wahner HW and Fogelman Ignac, *The evaluation of osteoporosis: dual energy absorptiometry in clinical practice*, Martin Dunitz, Ch 3, p23, 1994
9. Federal Register, Volume 69, Number 28, 11 February 2004
10. Wilson KE, Emerging trends in dual energy x-ray absorptiometry, Hologic Inc, W-159, 2006

About the authors



Annelee Spano Lander currently serves as Program Director of DXA Services with CoreLab Partners, where she oversees the development and day to day operations for the company's DXA Quality Assurance Program services. Prior to joining CoreLab Partners, Annelee was with PRA International where she served as a Senior Project Director for international full service clinical trials. Earlier in her career she spent several years with Synarc in roles of increasing responsibility, where she was a Global Project Manager and coordinated the collection and analysis of imaging data for numerous multi-centred, international trials. Annelee graduated from the University of Hawaii with a BS and continued on to earn her MS in education and statistics from the University of Portland. She is a member of several professional organisations including PMI and ASBMR.
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