Monitoring BMD with DXA: Short- and Long-term Precision

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ABSTRACT

The ability to monitor patient response to osteoporosis therapy with DXA depends on long-term *in vivo* precision and expected treatment response to therapy at a particular region.

A review of recent peer-reviewed literature (57 studies) of short-term *in vivo* coefficient of variations (CV's) found a statistically significant difference between manufacturers for the AP spine and femoral neck, but not for the total hip. The average CV of the three manufacturers at the AP spine was 1.08% for Hologic, 1.22% for GE/Lunar, and 1.58% for Norland. At the femoral neck the average CV was 1.50% for Hologic, 1.97% for GE/Lunar, and 2.30% for Norland.

Multiple studies have shown that the spine has two to three times the expected treatment response to osteoporosis therapy compared to the total hip or femoral neck, requiring hip precision to be two to three times better than AP spine to be useful for monitoring. However, when the peer reviewed literature was examined, there was no statistically significant differences between the CV's of the AP spine and total hip (mean CV's were 1.2% and 1.3%, respectively).

While short-term *in vivo* precision is often reported because it is easier to ascertain, it is long-term precision that is crucial for patient monitoring. While not a measure of long-term precision, seven studies (three using Hologic instruments, four using GE/Lunar instruments) did look at precision with repeat measurement done at least an hour later. These assessments, which more closely simulate clinical use, had an average CV at the spine of 1.2% for Hologic and 1.7% for GE/Lunar.

Hangartner monitored long-term precision on phantoms for three years on two Hologic and two GE/Lunar densitometers. All four instruments passed QC during the entire monitoring period. The total change of the two Hologic instruments was 0.01% and 0.13% during the three years, both of which are clinically insignificant. The two GE/Lunar instruments changed by 1.5% and -4.5% during the same three year time period, both clinically significant differences even though both scanners were within the manufacturer's allowed tolerances.

The long-term precision of Hologic instruments was also demonstrated in a pharmaceutical phase three study, where the average CV on phantoms was less than 0.5% for the thirty-four Hologic densitometers over a period of six years.

We conclude that the peer reviewed literature indicates that there are manufacturer differences in precision, and that these differences may be even greater for the clinically significant long-term precision than the less relevant short-term precision that is typically reported upon.

INTRODUCTION

The ability to monitor patient response to osteoporosis therapy with DXA depends on long-term *in vivo* precision and the expected treatment response to therapy at a particular region.

The technician's ability to reposition the patient and consistency in analysis methods is widely regarded as one of the major sources of error.[1] The *in vivo* short-term precision, as measured by a precision study where patients get off and then back onto the instrument, is sometimes used to determine the Least Significant Change (LSC) that is detectable. The International Society of Clinical Densitometry (ISCD) recommends that each technologist perform an
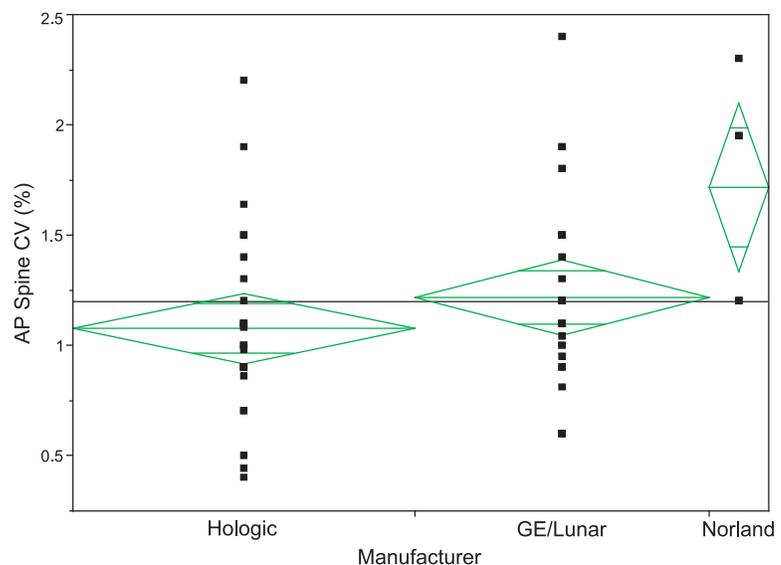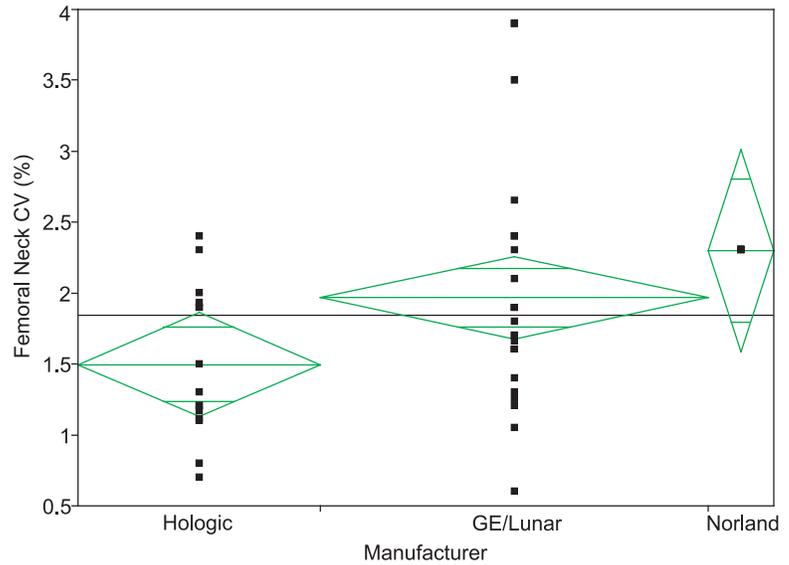

Figure 1: *AP spine CV (%) by manufacturer, diamonds indicate group mean*

in vivo precision study to determine the LSC for that technologist.[2]

While technologist performance is a significant contributor to precision, other sources of error may be of equal or greater importance in monitoring patients with DXA. This paper will review the literature and technology that relates to monitoring patients in a clinical environment. We will examine some of the recent peer-reviewed literature to determine if short-term precision is manufacturer dependent. We will examine in more detail whether short-term precision values, as measured by having a patient get on and off the table, are actually representative of the long-term precision, which is the relevant precision value for patient monitoring. And finally, we will look at the allowed and actual long-term drift of different manufacturer's densitometers and its effect on long-term precision.

Figure 2: *Femoral neck CV (%) by manufacturer, diamonds indicate group mean*

SHORT-TERM PRECISION

For the 2005 Position Development Conference, the ISCD Committee on Standards in Bone Measurements was asked to address the question of what is the maximum CV that would be acceptable at a given site; a CV value exceeding the maximum would indicate a need for technologist retraining. To address that question, the committee searched recent articles in *Calcified Tissue International, Journal of Bone and Metabolism, Journal of Bone and Mineral Research, Journal of Clinical Densitometry, and Osteoporosis International.* Precision is often reported in the "Material and Methods" section of articles in these journals without reference to precision in the keywords or abstract, so the journal's articles were reviewed by eye. Studies that reported *in vitro* precision studies or *in vivo* studies with very few degrees of freedom were excluded. Fifty-seven studies were identified.[3-59] In most of the studies precision was not the primary outcome variable, thus reducing, but not necessarily eliminating, reporting bias. Often times, there was very little reported other than the manufacturer of the instrument, its model and the CV. Because of a lack of consistent information regarding sample size, population characteristics, etc., it was necessary to summarize the data using descriptive statistics, instead of pooling the data.[60] Nevertheless, because of the large number of studies, the descriptive statistics were enlightening and was the basis for answering the question posed to the ISCD committee concerning the maximum CV that is acceptable. We will use this same set of studies to consider other questions regarding precision.

The studies in the review reported a relatively wide range of precision (see Figures 1 and 2). The median CV at the spine, total hip, and femoral neck for all studies was 1.10%, 1.20% and 1.85%, respectively. As expected, there was no clear trend of CV versus sample size. Though there was large variation in reported CV's from individual studies, examination using the statistical test of Wilcoxon / Kruskal-Wallis revealed significant differences at the 95% confidence level in CVs among manufacturers for AP spine and femoral neck (see Table 1) but not for the total hip[61].

There were too few studies to reach statistical significance between any two particular models of densitometer.

Table 1: *Average CV for different manufacturer's from peer reviewed studies[3-59] where the Wilcoxon/ Kruskal-Wallis test revealed a statistically significant dependence of the mean precision by manufacturer.*

Region	All manufacturers	Hologic	GE / Lunar	Norland	p value
AP spine	1.17%	1.08%	1.22%	1.58%	0.02
Femoral neck	1.85%	1.50%	1.97%	2.30%	0.03

However, at the AP spine, the mean CV for the twelve studies which used Hologic modern fan-beams (such as the QDR-4500, Delphi and Discovery) was 1.0%, while for six studies that used the latest GE/Lunar fan beam instruments (various models of Prodigy) the mean CV was 1.3%. These results are consistent with the results for all models of those respective manufacturers, which are reported in Table 1.

Most, but not all, of the reported studies measured *in vivo* precision by having the patient get off the table, and then immediately back onto the table. Though widely performed, this type of study is not necessarily a good estimate of the clinically relevant LSC. There were a few recent studies[4, 8, 16, 28, 31] (three Hologic and three GE/Lunar) in the survey that measured precision using a more realistic model where the first and second measurements were performed on a different day. The mean CV's at the AP spine for the three Hologic studies that used this more robust estimate were 1.1%, 1.4% and 1.1%, very close to the average of all Hologic studies of 1.08%. For the three GE/Lunar studies (one paper[28] measured long-term precision on both the DPX and Prodigy), the mean CV's at the AP spine were 1.4%, 1.5% and 1.9%, compared with the average of all GE/Lunar studies of 1.22%.

Since the survey by the ISCD subcommittee was completed, a large study (n=222) on precision performed in the Fall of 2004 using a Prodigy has been published.[62] This study measured precision with one hour to seven days between repeat measurements and found CV's for the AP spine of 2.0%. Again, this value is higher than the majority of somewhat artificial precision estimates performed on GE/Lunar instruments where the repeat measurement was done immediately after the first measurement.

Taken as a whole, there is the suggestion that precision may be worse when measurements are done in a more realistic manner (*i.e.* on different days), and that the size of the effect may be manufacturer dependent. To test this hypothesis, well designed studies which measure the precision using the same day method versus precision estimates based on measurements performed on different days (preferably one to two weeks separated) are needed using modern instruments and analysis methods.

SITE SELECTION FOR MONITORING

There has been some discussion about the best anatomical site for monitoring response to therapy. The ISCD recom-
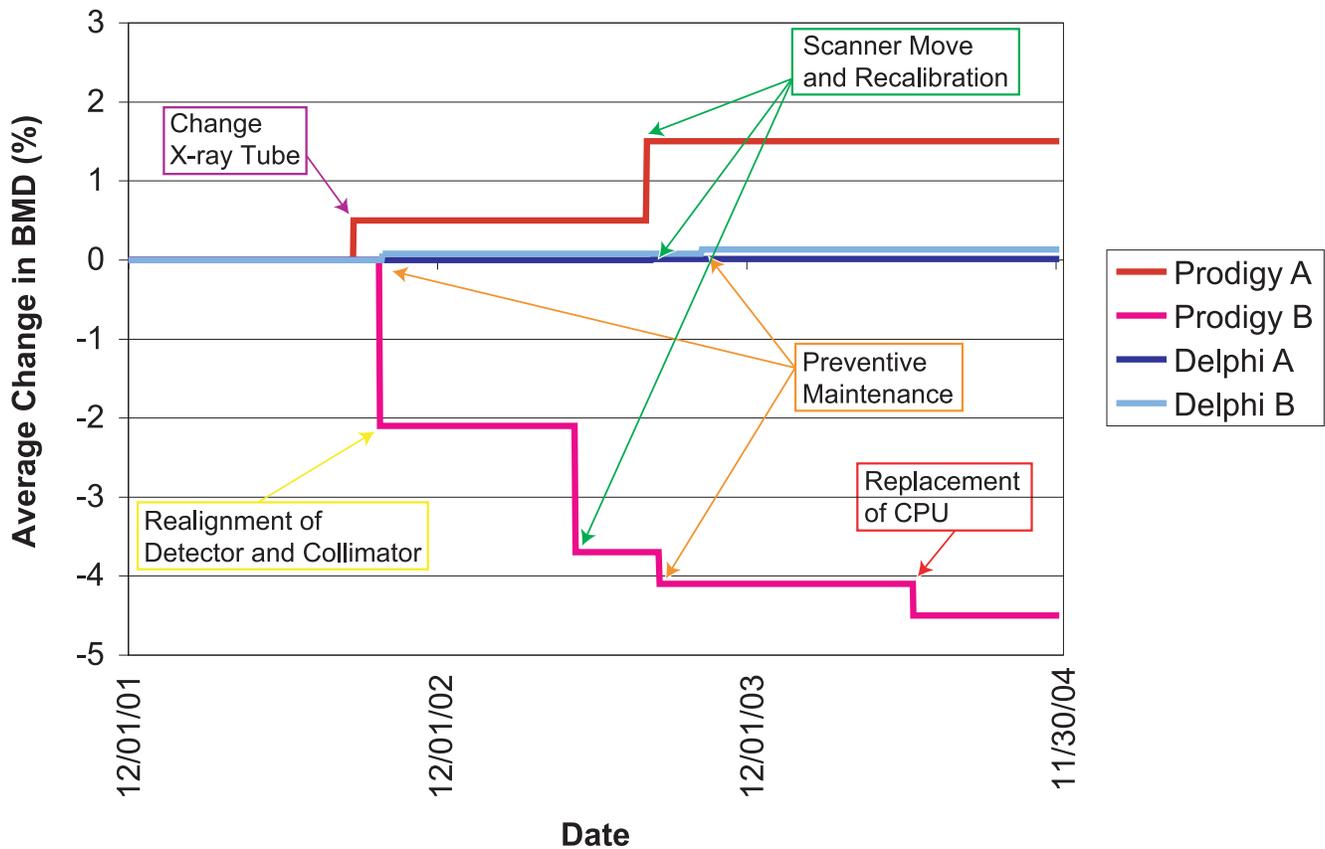
Long-term precision comparison

Figure 3: *Long-term precision comparison, adapted from Hangartner[67]*

mends the AP spine as the first choice, since treatment effects are larger at this site.[63] However, if the total hip had significantly better precision than the AP spine, this might be a reason to monitor at this site. When the recent peer reviewed literature was examined, there was no statistically significant difference in AP spine or total hip precision; the mean CV was 1.2% for the spine and 1.3% for the total hip.

Some have advocated "dual hip" exams to improve the ability to monitor changes in BMD. This is curious, since the expected change in treatment is about two to three times larger at the AP spine vs. the total hip.[64, 65] Measuring both hips, is expected to reduce the precision error by 30%. Since more change is expected at the spine and the precision of the spine and hip measurements are approximately the same, one could monitor change much more effectively by measuring the spine twice instead of measuring both hips. Another common justification for measuring both hips is for improved fracture prediction, but Blake *et. al.*[66] have shown that measuring both hips does not improve fracture prediction by a meaningful amount (the relative risk would go only from 2.60 to 2.63) because the two measurements are highly correlated. As Blake points out, to improve fracture risk prediction above a single BMD measurement, one must measure a quantity that is largely independent of BMD, such as prevalent vertebral fractures or biochemical markers.

LONG-TERM PRECISION

There are three important factors that are not captured in precision studies where the repeat measurement is performed immediately after the first. One of these is related to the human element; the other two are instrument dependent.

With respect to the human element, it seems highly probable that the technologist will more closely reproduce patient positioning if the repeat exams immediately follow one another, versus allowing several days or weeks between repeat exams. The patient learns what to expect, is wearing the same cloths providing visual clues, the technologist remembers what she has just done, etc. In a true clinical follow-up measurement a year later, none of these things are true.

Regarding possible manufacturer dependence, first, whenever an instrument has a daily or weekly calibration (as in the case of GE/Lunar and Norland), then the "on and off the table" experiment is fundamentally different from the baseline/follow-up measurement. This is because the baseline/follow-up measurement will be using a different instrument calibration, while the "on and off the table" uses the *same* instrument calibration. For Hologic instruments the situation is different because *each* scan is calibrated with the internal reference wheel. Thus the "on and off the table" experiment has two calibrations, exactly as in the baseline/follow-up measurement. Therefore, one may find that repeat measurements on separate days may have a man-

ufacturer dependent difference because of the different calibration methodologies.

Finally, in clinical medicine, the allowed instrument drift is critically important. Long-term drift is often monitored in research studies and final results are corrected for drifts above a predetermined amount (sometimes 1%, though some studies choose to correct smaller differences that are statistically significant). However, in clinical practice, most users do not correct for instrumental drift, but simply assume that a regular QC program will notify them if the instrumental drift is "significant", unaware that different manufacturer's have different allowed ranges for "acceptable" drift. This assumption was critically examined by Prof. Hangartner[67] over a three year period on two Delphi and two Prodigy DXA systems.

In Hangartner's experiment, all four instruments performed "within the manufacturer's specifications" during the study period. Hangartner used a specially designed phantom to monitor drift. He found that the two Prodigy's had calibration changes associated with service visits of 1.5% on Prodigy A and -4.5% on Prodigy B (see Figure 3). On the two Hologic instruments, he found that Delphi A maintained its stability, changing only 0.01% over the three year period. Delphi B changed only 0.13%; both changes were clinically insignificant. Examination of the machine specifications provides some insight into these disparate results. On the Prodigy, the instrument is allowed to have a result that varies ± 3% from the known phantom value (see Figure
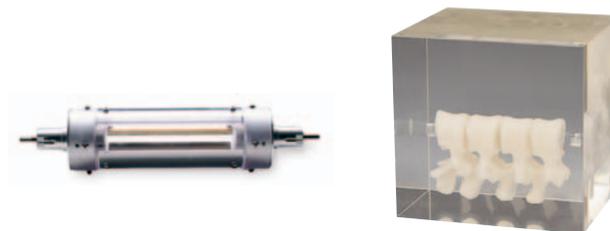
Figure 4: Hologic Internal Reference Wheel and Anthropomorphic Spine Phantom

Figure 5: GE/Lunar Spine Phantom

5). Thus Prodigy B started off at the high end of the allowed range, and moved over time to the low end of the allowed range. The allowed range on Hologic densitometers is ± 1.5%, or one-half the allowed range of Prodigy. Since LSC's measured by the on and off the table experiments recommended by the ISCD are typically only 2% – 4%, undetected long-term instrument drift represents a major under-appreciated problem in clinical practice.

The rock solid stability of the Hologic instruments is not the exception. In research studies, where long-term precision is critically monitored, Hologic modern fan-beams have an excellent record of long-term precision. For example, Perron *et. al.* reported on the long-term precision of thirty-four (34) Hologic modern fan-beam instruments over six years. They conclude that "the stability of all the QDR-4500 over 6 years remains very good with an average CV<0.5%".[68]

Hologic has recognized from the start that the clinically relevant precision is long-term precision. This is why from the beginning Hologic incorporated the internal reference wheel, the anthropomorphic spine phantom (see Figure 4) and strict daily QC protocols with the tightest BMD QC limits in the industry.

CONCLUSIONS

In conclusion, values obtained in short-term precision studies vary widely. However, taken as a whole, this review of fifty-seven studies in the recent peer-reviewed literature showed a statistically significant difference by manufacturer for the AP spine and femoral neck precision, with Hologic having the best short-term precision among manufacturers. As discussed, these short-term precision studies may not be reflective of the true Least Significant Change that is detectable over a one to two year period because there are manufacturer differences in instrument stability. Hologic's required stability is ± 1.5% and GE/Lunar's is ± 3.0% on manufacturer provided spine phantoms. In the Hangartner study, the actual BMD stability of the two Hologic systems (0.01% and 0.13%) exceeded the manufacturer's specifications, where as both GE/Lunar systems were considerably less stable (1.5% and – 4.5%). Further, the GE/Lunar instruments drifted amounts that are clinically significant, even though both densitometers were working within the manufacturer specifications. The large drifts documented in both Prodigy's significantly compromise the ability to monitor patients in a clinical setting.

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