Omnisense: At Least As Good As DXA

The following document summarizes a series of clinical studies that have been conducted to compare between different qualities of the Sunlight Omnisense™ (Omnisense) against the DXA technology. These studies support the claim that the Omnisense provides Osteoporosis diagnosis, which is at least as good as the DXA, and can serve as an alternative to the radiation-based traditional technology.

It is important to note that a comparison between a QUS (Quantitative Ultrasound) device – the Omnisense - and a DXA device is complex, as the two devices are based on two distinctly different technologies and measured parameters (i.e. Speed Of Sound and Bone Mineral Density).

However, since the diagnosis of Osteoporosis concerns ***assessment of fracture risk*** – and **not assessment of bone mass** – there is a basis for comparison, even when different technologies are involved. Hence, in order to compare the two technologies, one should examine the capability of each of them to assess risk of fracture, along with their relative advantages and disadvantages. This document will present data that support the claim that the Omnisense measurements can provide a valid estimate of osteoporotic fracture risk independently of BMD, and hence have a profound clinical value that is at least as good and may even be superior to that of the DXA.

DXA drawbacks

During the last two decades DXA has been used extensively, and has been accepted as a standard for estimation of fracture risk. However, it is neither a perfect nor an uncontroversial tool. The following are a few of the many technical limitations of the technology and problems associated with its diagnostic capabilities :

BMD discriminatory ability for fractures is not very high:
it can be found in literature that there is a large overlap between BMD measurements of non-fractured subjects and BMD measurements of fractured subjects. This implies that low-trauma fractures can occur at high, normal or low BMD, and suggests that factors other than BMD might be important for the occurrence of fracture[1].

Accuracy errors, especially in the case of Lumbar Spine BMD:
After the age of 60, falsely high values of spine BMD are encountered, due to various other diseases, such as vascular calcification and osteoarthritis. This might lead to misdiagnosis (false negative), and consequently, to a wrong decision regarding treatment.

Problems of reproducibility (precision errors):
Since a precision error can result either in wrong interpretation of BMD results or in a lack of ability to monitor bone changes, it is

highly important that a diagnostic tool has the lowest precision error possible. This is not so in the case of the DXA. For example, even in the case of a hip measurement, the patient might lie down in a slightly different angle – and thus cause the marking of a different ROI (Region of Interest) by the operator between two different examinations.

Discrepancies between different devices of the same brand:

There is a significant magnitude of inter-device variability between different DXA devices, even if they are of the same brand[2]. This implies that when even two devices of the same brand measure a patient in two different occasions (e.g. in two consecutive years) – one should refer to the results with caution. In the case of a new model of the same brand, there is normally no backward compatibility, so there is no reliable way to monitor a patient's bone change over time. Furthermore, unexpected accuracy errors can occur after machine repair, which are difficult to discover by the recommended operator's routine procedures[3].

BMD is not a good measure of bone strength: BMD is a crude expression of bone mineral concentration for a given area, not taking into account bone size or architecture. It is also influenced by body mass and growth, while true density (measured by BMC, for example) should not be influenced by these factors [4,5].

Omnisense Reference Database supports WHO criteria

This study[6] demonstrates that "*The RAD and PLX curves cross the T = -2.5 level, which is the WHO criteria for osteoporosis by BMD measured at any site, at about the age of 75, similar to Spine and Radius BMD T-score curves (QDR 1000 of Hologic Inc.,…)*". Specifically, it was shown, that the OP prevalence at the ages of 60-69 was higher than the one measured by femural neck DEXA, and ***similar*** to those known from the ***Vertebral and Radial BMD.***

Omnisense SOS is more informative than DXA's BMD

Definition: Osteoporosis is a systemic skeletal disease, characterized by reduced bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture, typically at the Hip, Spine, and Wrist[7].

The Omnisense is capable of reflecting more bone properties than merely density[8] as opposed to the traditional DXA technology, that measures solely Bone Mineral Density (or bone mass), The mechanical properties of the bone include, in addition to density, also elasticity, cortical thickness and micro architecture. All influence the strength of bone – which is reflected in the SOS measurements of the Omnisense. The deterioration of these properties may lead to Osteoporotic fractures.

Prof. Sievanen from Finland[9], proposes that the SOS data may represent the overall mechanical integrity of bone, and that "The unexplained part of the SOS is probably attributable to microarchitecture and elastic properties of given bone…".

Omnisense can predict Hip fracture in a study conducted in Beth Israel Deaconess Medical Center and Harvard Medical School [10], it was demonstrated that the SOS measurement at the Radius performed by Omnisense can be used in predicting femoral failure load, with a similar predicting power to that of the DXA Hip measurements. The high reproducibility (low precision error) of the Radius is suggested by the authors as one of the explanations to this site's good predictive performance.

Omnisense has better sensitivity than DXA

Due to the nature of the disease, until today no absolute test has been developed to determine the presence of Osteoporosis in the case of a specific patient. The only indisputable case for having Osteoporosis is in the presence of a low trauma fracture. This is obvious evidence of the disease.

The following classification studies are based on this exact concept: A group of fractured subjects (with low-trauma fractures, namely: subjects who clearly suffer from Osteoporosis) was measured by different devices (both DXA and Omnisense), to determine the presence of the disease. This investigation method was used as a way to evaluate the sensitivity of each device, by looking at the percentage of subjects who were classified as Osteoporotic, according to the WHO criteria (T-score < -2.5). A "normal" result meant, of course, misdiagnosis (false negative).

It was found that the Omnisense classified a higher percentage of subjects with Osteoporotic fractures as Osteoporotic, than the DXA. In other words, the **DXA had a higher rate of misdiagnosis.**

Omnisense classifies more fractured patients as osteoporotic than DEXA, using to the WHO criteria In classification studies, it has been found that the Omnisense classifies more people with different Osteoporotic fractures as having Osteoporosis, than the DEXA. In other words, the DEXA had a higher rate of misdiagnosis.

Better classification than DXA

This trend is clearly demonstrated in a study that was conducted in a well-known hospital (the study is now being prepared for publication). Among all fractured patients who were measured by the Omnisense and with DXA, many more subjects were misdiagnosed (as being "normal") by the DXA:

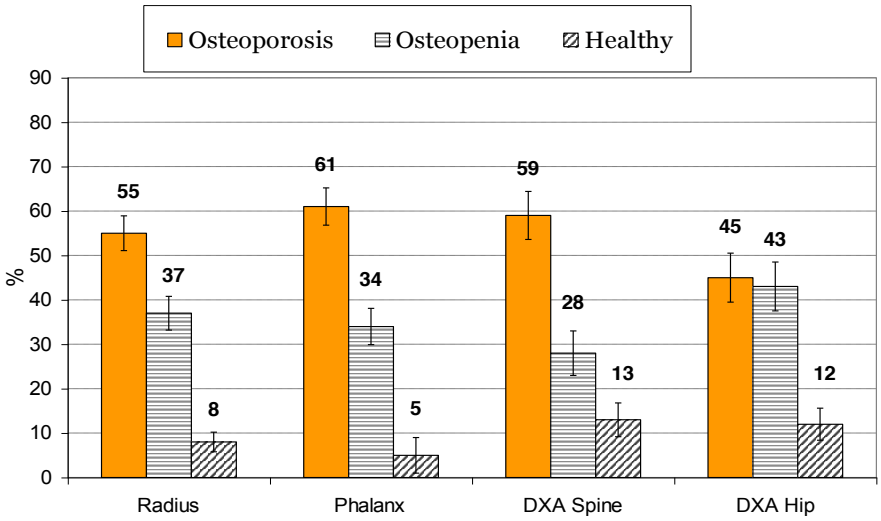

Figure 1 – WHO classification for approximately 150 fractured, with different fractures (Hip, Spine, Wrist) - percentage

Similar results were obtained, when dividing the data into groups according to type-of-fracture. Furthermore, when the Minimal T-score criterion* was applied (for measurements in multiple skeletal sites), both the Omnisense and the DXA improved their sensitivity – but the Omnisense had better results. Table 1 presents percentage of misclassification (fractured that were classified as healthy, T-score>-1, using the WHO criteria):

Fracture Type	***Radius (%)***	***Phalanx (%)***	***DXA Spine (%)***	***DXA Hip (%)***	***Min DXA* (%)***	***Min R.&Ph. (%) ****

*Minimal T-score principle: Each patient was measured at two sites with both the Omnisense and the DXA. The sites were Hip & Spine in the case of DXA and Radius & Phalanx – for the Omnisense. The *minimum T-score principle* was determined by the lower T-score result received for both sites on the same device, and was used to define the subject's classification, whether Osteoporotic, Osteopenic or Normal.

HF	7	4	12	4	0	**1**
VF	8	5	11	16	5	**0**
WF	7	6	19	16	10	**0**
All fractures	8	5	13	12	6	**1**

Table 1 – Percentage of misclassification when using measurement results of different sites by Omnisense & DXA, including Minimal T-score parameter (where: HF, VF, WF are Hip, Vertebral and Wrist Fractures, respectively; R. & Ph.=Radius and phalanx)

Applicability of WHO criteria: Omnisense Reference DB of 4 sites

The following presents a retrospective comparison of Omnisense and a few other diagnostic devices' different Reference Data curves. The Omnisense Reference database[11] demonstrates that "The Radius and Phalanx curves cross the T = -2.5 level, which is the WHO criteria for osteoporosis by BMD measured at any site, at about the age of 75, similar to Spine and Radius BMD T-score curves (QDR 1000 of Hologic Inc.)". Specifically, it was shown, that the Osteoporosis prevalence at the ages of 60-69 was higher than the one measured by femoral neck DXA, and **similar** *to those known from the* **Vertebral and Radial BMD** *(see Figure 2).*

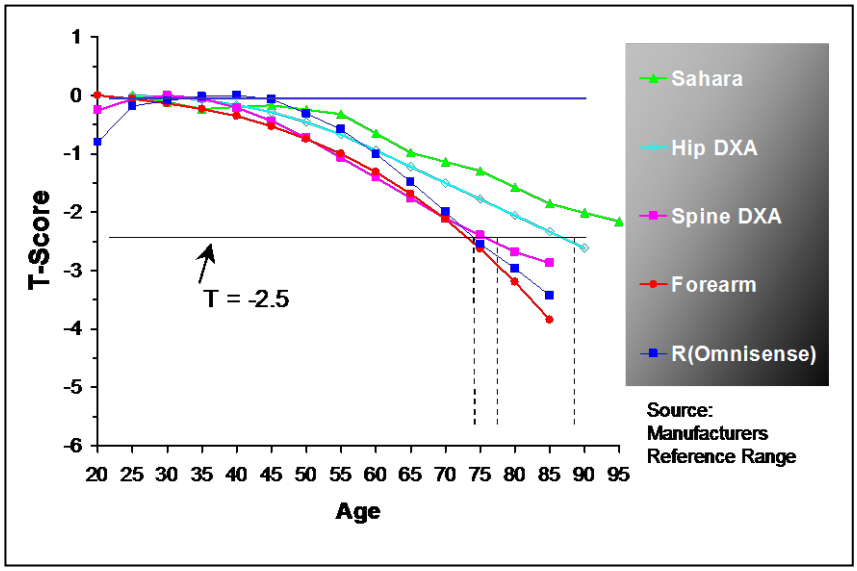

Figure 2 – Comparison between normative reference database of different devices (applicability of WHO criteria)

Omnisense discriminates between population groups at least as well as the DXA

Different publications deal with the discriminatory power of the Omnisense. This is defined as the ability to discriminate between post-menopausal women with osteoporotic fractures and two other groups: pre-menopausal (Young, Healthy) and post-menopausal age matched non-fractured controls. The following results demonstrate the discriminatory ability of the Omnisense, compared to that of the DXA.

Vertebral fractures discrimination:

Knapp et al. reported the results of vertebral fracture discrimination at the ASBMR 21st Annual Meeting[12]. **The measurements at the radius were found to have similar differentiation power to those of DXA of the spine**.

Colles' fracture discrimination:

The same authors have presented another abstract[13] (the Bone and Tooth Society Meeting, Bristol, UK, June 1999) regarding the prediction of wrist fractures. Their results suggest that the ***Omnisense SOS measurements of the radius are at least as good as those of DXA in separating wrist fracture patients from controls.***

Results	Z-score	OR*	p value
SOS Radius	-0.97	2.45	0.01
DXA L1-L4	-0.59	1.43	ns
DXA Neck of Femur	-0.60	1.24	ns
DXA Total Hip	-0.90	1.94	0.05

Table 2 – measurement results at the Radius (SOS) and by the DXA at various sites

Hip fracture discrimination:

This type of fracture group was also measured by the Omnisense to determine its discriminatory ability[14]. **Significant differences between fractured subjects and age-matched controls was found**. This study did not contain comparison to DXA measurements.

Monitoring bone changes following treatment

Several retrospective studies were conducted to evaluate the Omnisense ability to detect bone changes following treatment, beginning with Hormone Replacement Therapy (HRT), which is a well-recognized treatment for the prevention of osteoporosis. It was found that the Omnisense is clearly able to discriminate between treated subjects and age-matched non-treated controls. Moreover, when the same subjects are measured by DXA there was a much smaller difference between the groups.

HRT bone influence: two studies

A study conducted by Knapp et al.[15] (Guy's Hospital & St. Thomas Hospital, London, UK) examined the ability of the Omnisense measurements at the Radius and the Tibia to differentiate between subjects receiving HRT and age matched controls. It was found that despite the small size of study groups, "***the QUS measurements demonstrate significant and relatively large differences (in units of T-scores) between the two subject groups***. ***DXA measurements*** … ***show less than half the difference between the groups, none of which achieving statistical significance***".

In another study[16] of a similar type, the Omnisense demonstrated significant discriminatory ability (Table 3), and more women in the non-treated group were found to be Osteoporotic. ***This demonstrates the device's high sensitivity to bone change as a result of treatment***.

Age Group	Treated Women	Non-treated subjects
50-60	2%	10%
60-70	15%	36%

Table 3 – Percentage of women with T-score below (-2.5) in each measured group

Group discrimination following HRT use: Data Analysis

An internal clinical data analysis was conducted on subject groups that were measured by the Omnisense and/or by DXA (all female Caucasians, from a similar environment). Calculations were done to adjust age or years from Menopause between the 2 groups, the same inclusion/exclusion criteria were applied, and Figure 3 clearly demonstrates that the results confirm those achieved in the studies previously mentioned (Paragraph 0 above).

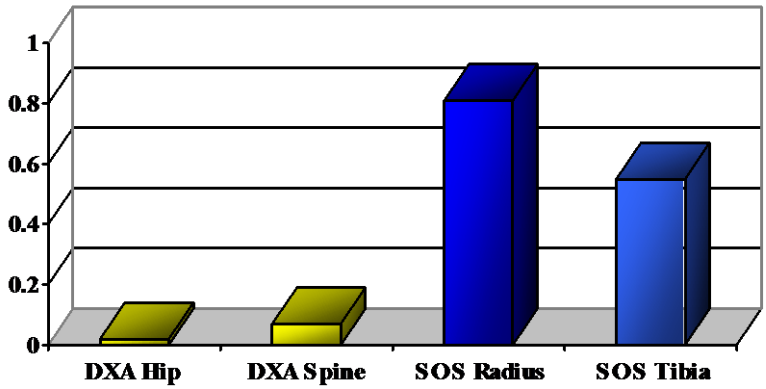

Figure 3 - T-score differences between HRT-treated women and non-treated women; comparison between DXA & Omnisense, after controlling for age or years after menopause

Omnisnese's measurement precision is higher than the DXA

On the basis of the conducted research studies, a measurement was made of several parameters that were indicative of Omnisense's precision level.

- In vivo precision of the Omnisense was calculated[17] as the coefficient of variation based on repeated measurements on pre and postmenopausal subjects (Intra Operator CV): Radius – 0.4%, Phalanx – 0.81%, Metatarsal – 0.66%. The Inter-operator CV was 0.8% at the Radius, and 1.4% at the Metatarsal and the Phalanx. These data indicate a very high reproducibility of measurements, and thus – a high reliability of the device.

- One of the indices that is commonly used to compare between precision levels of different devices, is the SCV (standardized CV). The Omnisense's SCV (1.8) is much lower than the DXA's (2.3)[18], based on publicly available information provided by manufacturers as part of FDA PMA application.

The indication in its FDA PMA approval confirms that "the SOS measured by Omnisense has a precision error low enough in comparison with the expected annual changes in a patients' measurement to make it suitable for monitoring bone changes which occur in the early years following menopause (i.e., age range approximately 50-65 years)"[19].

Omnisense detects changes in bone status caused by other diseases, while DXA has lower sensitivity

It was demonstrated[20] that the **Omnisense is capable of clearly discriminating between 3 population groups: euthyroid, hyper and hypothyroid patients.** Both hyper and hypothyroid had statistically significant lower SOS results at all 3 sites measured (radius, tibia and metatarsal).

It is previously known that hyperthyroid patients suffer from secondary Osteoporosis. While DXA had lower sensitivity to those cases, Omnisense could single them out. Furthermore, in the case of hypothyroidism, it was suggested that interstitial fluid that may accumulate inside the bone slows down the propagation of the ultrasonic wave.

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[1] Pors Nielsen, "The Fallacy of BMD". In press.
[2] Formica C A, "Standardization of BMD measurements." Editorial. Osteoporosis Int. 1998; 8: 1-3.
[3] Blake G M et al., "An unexpected change in DXA calibration not detected by routine quality control checks." Osteoporosis Int 1999; 9:115-120.
[4] Ott S M et al, "Evaluation of vertebral volumetric vs. areal bone mineral density during growth." Bone 20:533-556.
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[7] Kanis et al., "Guidlinges for diagnosis and management of osteoporosis", Osteoporosis Int 1997; 7: 390-406.
[8] Pors Nielsen et al., "Colles' fracture: Cross-sectional properties of the distal radius" In Press.
[9] Sievanen H, and the Bone research Group at the UKK Institute in Tampere, Finland "QUS Derived Speed of Sound and Cortical Bone Structure", (abstract) presented at the ASBMR 21st Annual Meeting in St. Louis, MI, USA, September 1999.
[10] Bouxsein, ML et al., "Prediction of Femoral Failure Load from Femoral BMD and Ultrasonic Velocity at the Femur, Radius and Phalanx" (abstract), presented at the ASBMR 21st Annual Meeting in St. Louis, MI, USA, September 1999.
[11] Weiss M, Ben Shlomo A, Hagag P, Rapoport M, "Normative Speed of Sound Database of a Novel Quantitative Multi-site Ultrasound Device", abstract presented at the ASBMR 21st Annual Meeting in St. Louis, MI, September 1999. Also: Osteoporosis Int., In press.
[12] Knapp et al. "Multiple Site Ultrasound Measurements Predict Vertebral Fractures in Postmenopausal Women" (abstract), ASBMR 21st Annual Meeting in St. Louis, MI, USA, September 1999.
[13] Knapp et al. "Ultrasound Measurements at the Radius Predict Wrist Fractures in Postmenopausal Women" (abstract), the Annual Meeting of the Bone and Tooth Society in Bristol, UK, June 1999.
[14] Weiss M, Ben Shlomo A, Hagag P, Ish-Shalom S. "Assessment of proximal hip fracture risk by quantitative ultrasound measurement at the radius". Osteoporosis Int, In press.
[15] Knapp, K et al. "Quantitative Ultrasound Measurements Detect Skeletal Changes in Cortical Bone Following HRT Use" (abstract), presented at the 11th International Workshop on Calcified Tissues, Eilat, Israel, February 1999.
[16] Weiss M et al. "HRT – SOS Changes as Reflected by the Sunlight Omnisense Measurements" (abstract), the 1st Congress on Controversies in Obstetrics Gynecology & Infertility, Prague, Czech Republic, October 1999. Also: submitted for publication to Maternitus.

[17] Weiss M et al., "The impotance of precision – new hopes for monitoring osteoporosis treatment by QUS" (abstract), submitted to ISCD 2000.

[18] SCV calculation is as follows: SCV1 = Standard Deviation / 0.95 * ($max_{sos} - min_{sos}$). DXA SCV (Hologic's QDR 1500) - adapted from Lunar's Summary of Safety and Effectiveness (SSE), submitted to the FDA. The comparison between the different devices was performed on different populations.

[19] Sunlight Omnisense™ FDA PMA (Pre-Market Application) approval, January 20, 2000.

[20] Ben Shlomo A, Weiss M et al., "Thyroid Dysfunctional State Detected by QUS Measurement at Multiple Skeletal Sites" (abstract), presented at the ASBMR 2nd Joint Meeting, California, USA, December, 1998. Also In Press.