# Technology Sheet

# EchoS

EchoS is the very first radiation-free solution for bone characterization and micro-architecture assessment. Its innovative approach enables the scanning of central reference sites:

**LUMBAR VERTEBRAE**
**PROXIMAL FEMUR**

# R.E.M.S. TECHNOLOGY

## Radiofrequency Echographic Multi Spectrometry

EchoS is based on the new and proprietary R.E.M.S. (Radiofrequency Echo-graphic Multi Spectrometry) method: an innovative ultrasound (US) approach, which integrally exploits all the spectral features of the “raw” radiofrequency (RF) signals acquired during an echographic scan of the target anatomical site to determine the status of internal bone architecture.

Watch the video

# Acquisition Protocol

To perform the diagnostic investigation (2 minutes), the operator should preliminarily visualize the first target interface (i.e. vertebra L1 for lumbar acquisitions or femoral neck for hip scans) and set acquisition parameters - depth and focus – in order to have the target interface in the central part of the image and in correspondence with the focus line.

Afterwards, the software-assisted US acquisition starts. During the scan, the algorithm automatically detects the bone interfaces and calculates the ROIs for data analysis (green areas). The automatic data processing is then started, including RF signal analysis and spectral comparison with reference models for the calculation of diagnostic parameters and generation of the final medical report.

Watch the demo

# Diagnostic Output

The automatic combined analysis of B-mode images and corresponding RF data provides two novel parameters: the Osteoporosis Score (O.S.), which is directly correlated with BMD, and the Fragility Score (F.S.)*, which quantifies the actual bone strength by assessing structural fragility independently from BMD. The medical report contains all the standard parameters for Osteoporosis diagnosis through bone density assessment:

**BMD (g/cm$^2$)**
**T-Score**
**Z-Score**

**FRAGILITY SCORE***

**BODY COMPOSITION***

Medical Report

*(*Fragility Score and Body Composition Index are not yet available in USA)*

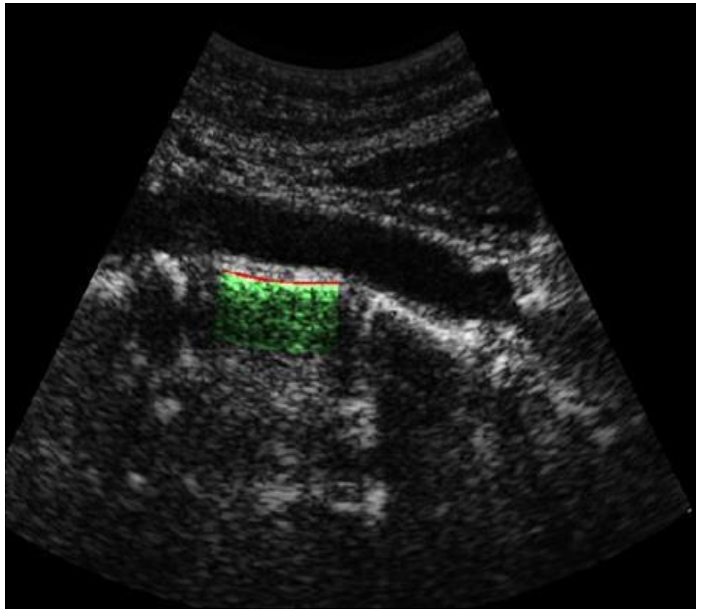
# Innovative Approach

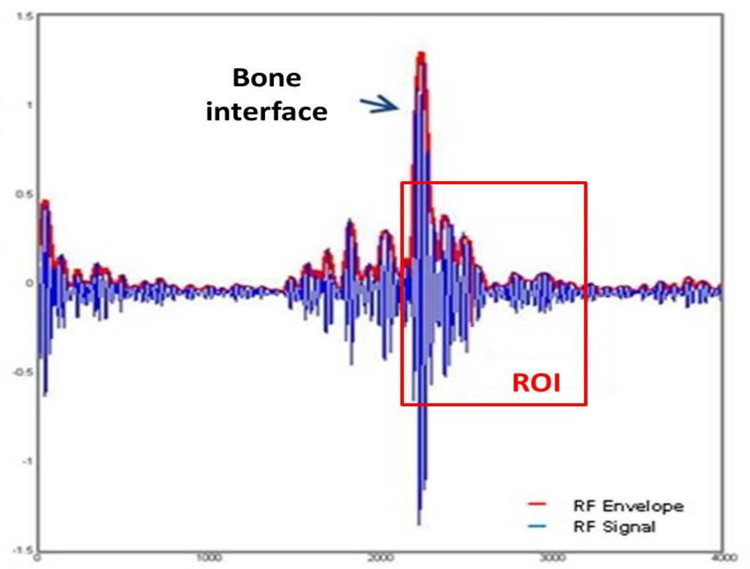
Echographic scans are performed by EchoS device equipped with a convex transducer operating at 3.5 MHz, allowing the simultaneous acquisition of conventional B-mode images and corresponding unprocessed RF signals.

R.E.M.S. approach is based on the idea that RF signals, acquired during an echographic scan of a target bone district, can be used to determine the health status of the considered bone through advanced comparisons with previously derived reference spectral models of the possible pathological or normal conditions.

This method is natively integrated with US imaging, since, on one hand, the regions of interest (ROIs) for diagnostic calculations within the investigated bone are automatically identified exploiting both morphologic details and RF spectral features, and, on the other hand, the simultaneous acquisition of several RF scan lines for each image frame provides a solid and reliable statistical basis for subsequent spectral processing.

Data analysis includes the calculation of the O.S. value and the F.S.* value, based on the correlation between frequency spectra of acquired RF signals and the appropriate reference models selected from “osteoporotic/healthy” and “fractured/not fractured” bones, respectively. BMD, T-score and Z-score are then derived from the O.S. value.



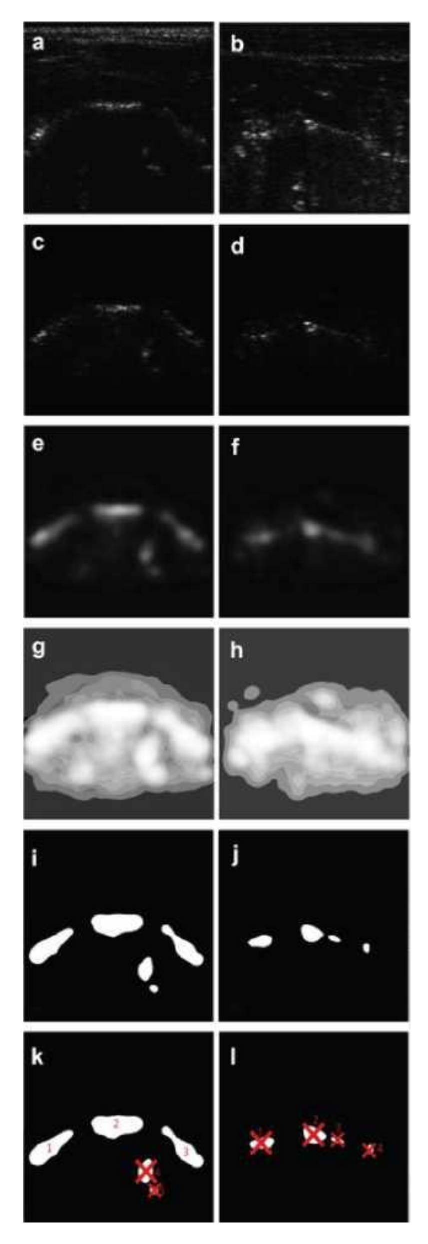



*(*Fragility Score is not yet available in USA)*

# Image Analysis

Automatic Identification of Target Bone Structures: the first operation carried out by the algorithm is the automatic identification of the target bone interfaces within the sequence of echographic images acquired on the considered patient.

Watch the demo




(a,b) Rearrangement of image data in rectangular matrices from the original sectorial images: (a) echographic image sample containing a vertebral interface that will be automatically identified, (b) "noisy" echographic image sample that will be automatically discarded because there are no suitable vertebral interfaces.

(c,d) Brightness masking

(e,f) Contrast enhancement and image smoothing

(g,h) Histogram equalization

(i,j) Thresholding

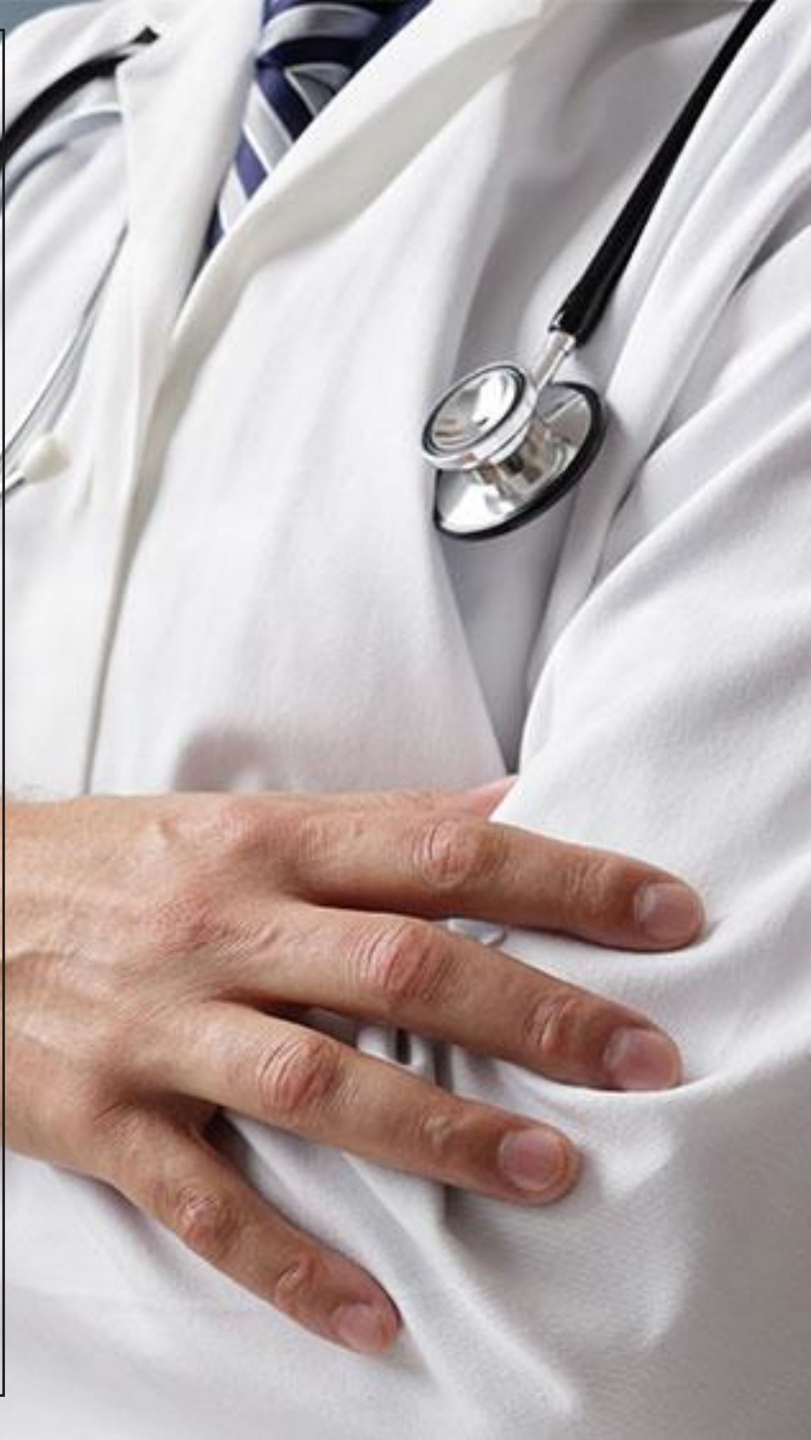
(k) clusters 4/5 are excluded because they are outside the expected size range for a vertebral interface, whereas clusters 1–3 are retained, and, after finer morphologic evaluations, cluster 2 is labeled as a ‘‘possible vertebral interface’’, whose nature will be verified through a dedicated spectral analysis; (l) all the clusters are excluded because they are outside the expected size range, and the frame is discarded.

# Spectral Comparison

Diagnostic parameter calculations are actually performed on RF signal segments corresponding to specific ROIs, which are automatically selected taking into account the position of the identified bone interfaces within the B-mode image. The principle behind is that the spectra of “raw” RF signals backscattered from the bone interface during an “in-vivo” echographic scan contain useful information about the bone status, including both quantity (e.g. BMD) and quality (e.g. elasticity) parameters.

Accordingly, the O.S. value measures the degree of similarity between RF spectra obtained from the considered patient and reference spectral models previously derived from both subjects with a low BMD (T-score ≤ -2.5) and subjects with normal BMD (T-score ≥ -1.0); on the other hand, the F.S.* value evaluates an analogous spectral similarity with subjects that reported a recent fragility fracture compared to control subjects without fracture history. In this way, each spectrum belonging to the identified ROIs undergoes an overall comparison with two pairs of sex-, race- and age-matched reference models that had been calculated from a database of real subjects.

*(*Fragility Score is not yet available in USA)*



# Osteoporosis Score

Once all the frames belonging to the US dataset of the patient have been analyzed, the system verifies if the number of detected interfaces is sufficient to obtain a reliable diagnosis and calculations are performed on each RF spectrum of the identified ROIs. If this minimal frame condition is not satisfied (it happens rarely), the dataset is labeled as ‘‘noisy’’ and the operator is asked to repeat the US scan. For the O.S. calculation, the considered RF spectrum is classified as ‘‘osteoporotic’’ if the value of its Pearson correlation coefficient with the appropriate osteoporotic model spectrum is higher than the corresponding value with the related healthy model spectrum, otherwise, it is classified as ‘‘healthy.’’ The percentage of the analyzed spectra classified as ‘‘osteoporotic’’ represents the O.S. value of the analyzed ROI.

The O.S. values of all the ROIs belonging to the same bone target (i.e. the same vertebra or the same femoral region) are then averaged to obtain the O.S. value of the considered bone structure. The same evaluations are repeated for each identified bone target, and the final O.S. is the average of the single values.

# Fragility Score*

An analogous procedure is simultaneously applied to calculate the F.S.* value, with the only difference being that “osteoporotic” and “healthy” reference models are replaced by the corresponding spectral models of “frail” and “non-frail” bone structures.

An important feature to be highlighted is the extreme ease of use of the system: inexperienced operators, who previously received a 3-hours specific training session only, performed acquisitions of a quality level appropriate for diagnostic calculations in 96.3% of cases (i.e. the incidence of “noisy” datasets was limited to 3.7%, and all of them became of suitable quality at a second scan).

*(*Fragility Score is not yet available in USA)*

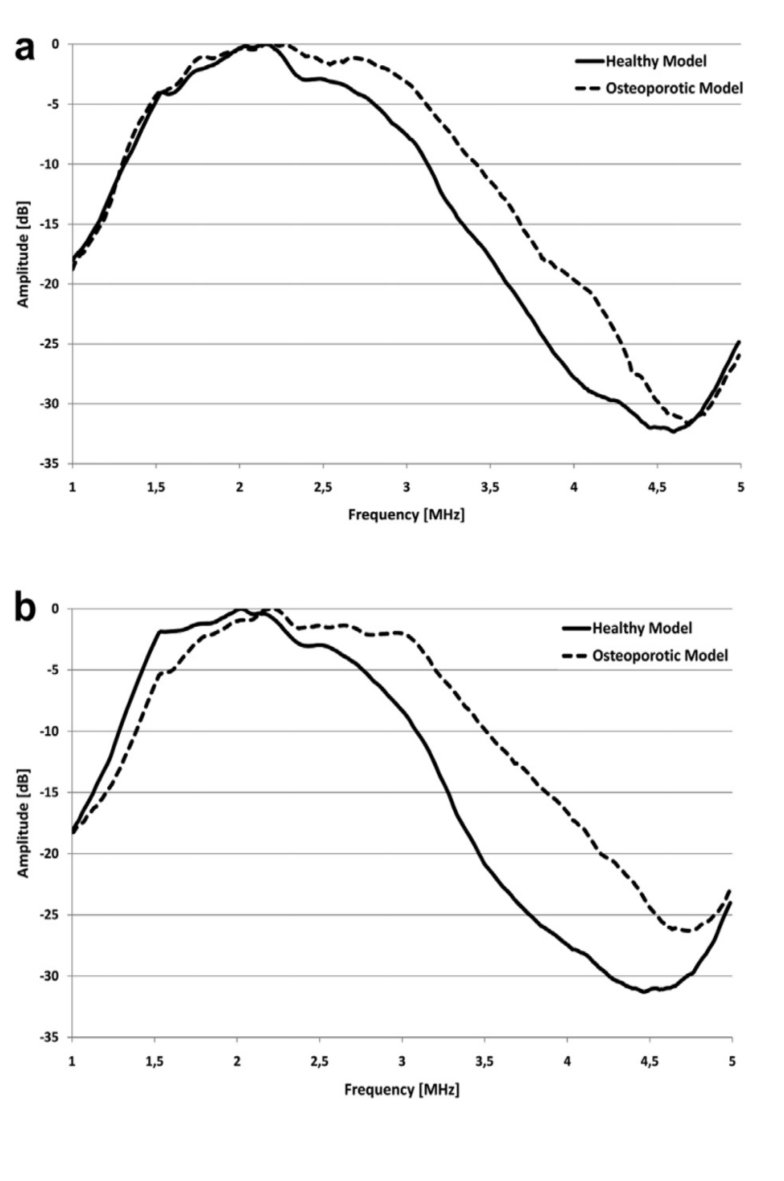
# Statistical Analysis

Current database version includes more than 10.000 subjects, covering the whole interval of typical BMI values, from under-weight to obese individuals. Subjects were grouped into 5-y intervals and, for each age interval, they were further split into three subgroups based on their BMI (i.e. under-weight/ normal-weight, over-weight, obese). For each obtained subgroup, the first 100 individuals were included in the reference database.

The subjects were recruited through international multicenter clinical studies involving hospitals and clinics specialized in osteoporosis diagnosis. All the subjects underwent the following diagnostic examinations: DXA scan of lumbar spine and/or proximal femur, TBS calculation where applicable, echographic scan of the same anatomical districts performed with EchoS system, FRAX® questionnaire.

In each identified subgroup, these data were used to calculate the corresponding pairs of reference spectral models for the following bone conditions: “osteoporotic/healthy”, assessed through the O.S. value, and “fractured/not-fractured”, assessed through the F.S.* value. All the obtained models were also included in the database and associated to the relevant subgroups. *(*Fragility Score is not yet available in USA)*

*Picture: Sample of reference model spectra for the calculation of O.S. value on lumbar spine. Pairs of “osteoporotic” and “healthy” spectral models obtained from two different subgroups of female subjects: (a) under-weight and normal-weight women aged 51-55 y; (b) under-weight and normal-weight women aged 56-60 y.*



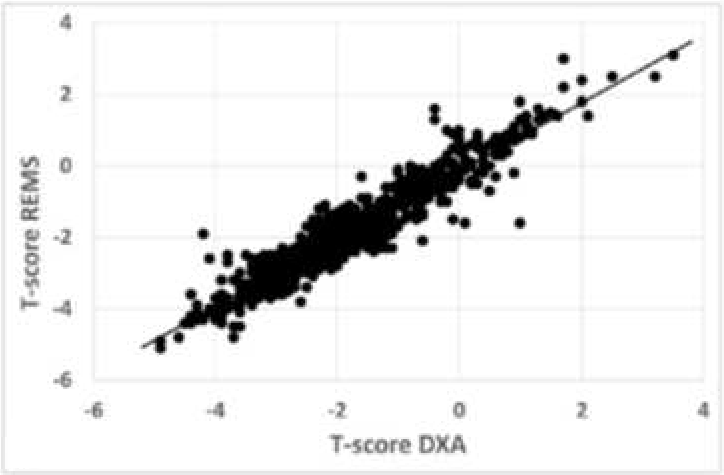
## Clinical Validation

## BMD

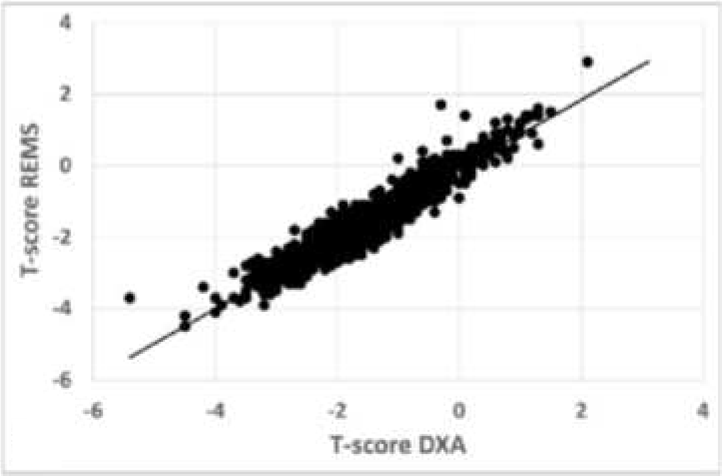
Diagnostic accuracy of the technology has been clinically assessed according to international scientific frameworks. More than 10.000 patients underwent DXA scans, EchoS echographic scans of the same anatomical districts, and FRAX® questionnaire for the estimation of fracture risk. BMD values derived from O.S. calculation were compared with the results of DXA measurements.

Literature

Lumbar Vertebrae




Proximal Femur



# Clinical Validation

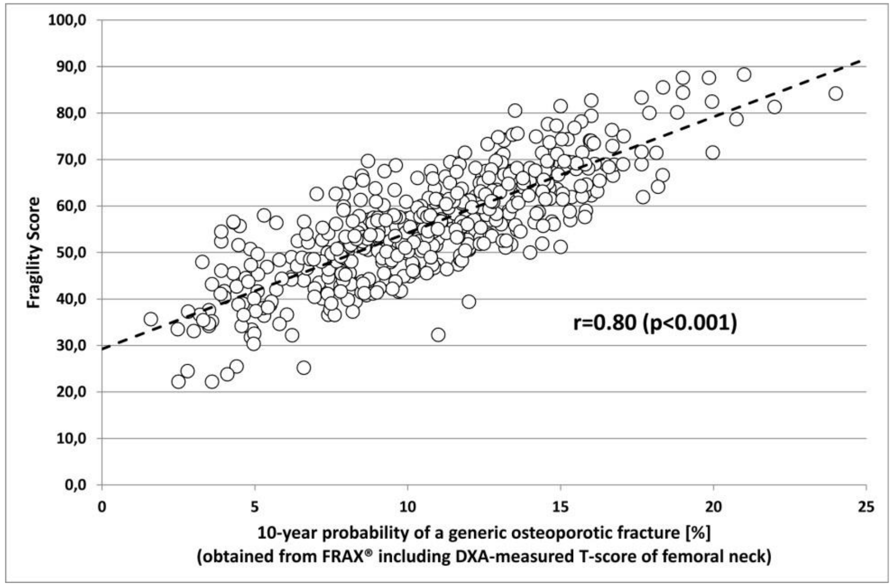
## Fragility Score

Fragility Score* values were compared to FRAX® predictions of 10-year probabilities of a generic osteoporotic fracture (calculated with the inclusion of DXA-measured femoral neck T-score).

Fragility Score*, derived from the same US data acquired for bone density assessment, showed a strong correlation with FRAX® fracture risk, whose calculation requires the answers to the FRAX® questionnaire and a DXA scan of femoral neck.

Literature

*(*Fragility Score is not yet available in USA)*



# Performance

| Vertebrae | PRECISION AND REPEATABILITY | Femur |
|---|---|---|
| **REMS** | **PARAMETER** | **REMS** |
| 0.009 g/cm² | SMALLEST DETECTABLE DIFFERENCE (SDD) | 0.006 g/cm² |
| 0.38 % | INTRA-OPERATOR REPEATABILITY (RMS-CV) | 0.32 % |
| 0.54 % | INTER-OPERATOR REPEATABILITY (RMS-CV) | 0.48 % |
| 1.05 % | LEAST SIGNIFICANT CHANGE (LSC,%) | 0.88 % |
| >90 % | DIAGNOSTIC AGREEMENT WITH DXA | >90 % |

| TECHNOLOGY COMPARISON | DXA | QUS | REMS |
|---|---|---|---|
| Radiation Exposure | YES | NO | NO |
| Axial Sites | YES | NO | YES |
| Bone Density ($g/cm^2$) | YES | NO | YES |
| Bone Quality | NO | NO | YES |
| Operator Independent | NO | NO | YES |
| Patient Positioning Influenced | YES | YES | NO |
| Soft Tissue Influenced | YES | YES | NO |
| Operator Certified Needed | YES | NO | NO |
| Dedicated Shield Room | YES | NO | NO |
| Maintenance Costs | YES | NO | NO |
| Diagnostic Tool | YES | NO | YES |
| Prevention, Monitoring and Follow-up | NO | NO | YES |

# Conclusions

The peculiar feature of R.E.M.S method is the exploitation of RF signals acquired during an echographic scan of the target bone structure to determine the internal bone architecture through detailed comparisons with reference spectral models. Another important feature of the technology is its full automation, which reduces to a minimum the dependence on operator experience. In fact, the implemented algorithm automatically identifies and discards “noisy” acquisitions, ensuring that diagnostic evaluations are performed only on US datasets reaching a specifically determined quality threshold. The extreme ease of use of the described system has also been demonstrated, together with its compliance with time constraints of clinical routine, since each patient can be examined and diagnosed in less than 2 min.

Because of its accuracy levels, combined with the complete absence of ionizing radiation and the proven ease of use, this method can be effectively employed for diagnosis of osteoporotic disease at an earlier stage. Moreover, the US assessment of internal bone structure not only gives information related to BMD, but also provides further insights into the structural quality of bone and its real strength, offering a simultaneous, independent and accurate prediction of fracture risk. The integration of all these features makes R.E.M.S method the future state-of-the-art approach for bone health assessment and the early diagnosis of Osteoporosis.

Reference Sites

# Echolight S.p.a.

A growing med-tech company located in Italy, in less than three years has built a sales network of 40 distributors and several hundreds of satisfied customers all over the world.

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ISO 13485

National Research Council of Italy

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