Beyond BMD

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Disclosure

- No direct compensation from potentially conflicting entities
- Employed by New Mexico Clinical Research & Osteoporosis Center, which has received the following in the past one year:
  - Research grant support from Amgen, Radius, Mereo
  - Consulting and scientific advisory board fees from Amgen, Radius, Alexion, Sandoz, Samsung Bioepis
  - Honoraria for speakers' bureaus of Alexion, Radius
  - Support for project development with University of New Mexico
  - Royalties from UpToDate for sections on DXA, fracture risk assessment, and prevention of osteoporosis
- Board positions with the NOF, ISCD, OFNM
- Guideline committees with NOF, ISCD, AACE, NAMS

Objectives

- Describe the technology and potential clinical applications of Pulse-Echo UltraSonography (PEUS)
- Describe the technology and potential clinical applications of Radiofrequency Echographic Multi-Spectrometry (REMS)
- Describe the technology and potential clinical applications of Impact Microindentation (IMI)

Pulse-Echo UltraSonography (PEUS)

PEUS Device

Bindex® BI-2 Device. Bone Index Finland, Ltd, Kuppio, Finland

- Non-invasive ultrasound technology
- Handheld transducer placed over proximal anterior tibia using ultrasound gel
- Signals transmitted to connected laptop/PC
- Cortical thickness is estimated by measuring lag time between ultrasound echoes from front and back surface of cortex

Image from Lewiecki EM. J Clin Densitom. 2021;24:175-182.

PEUS Technical

- Location on tibia is standardized to one-third the length from the proximal head of the tibia to the medical malleolus
- Transducer generates 3.0 MHz ultrasound waves
- 5 measurements, averaging total of 5 minutes
- Density Index (DI) calculated with input of cortical thickness, age, weight, and height to generate a value that is correlated with total hip BMD

Lewiecki EM. J Clin Densitom. 2021;24:175-182.

ISCD Official Positions: QUS

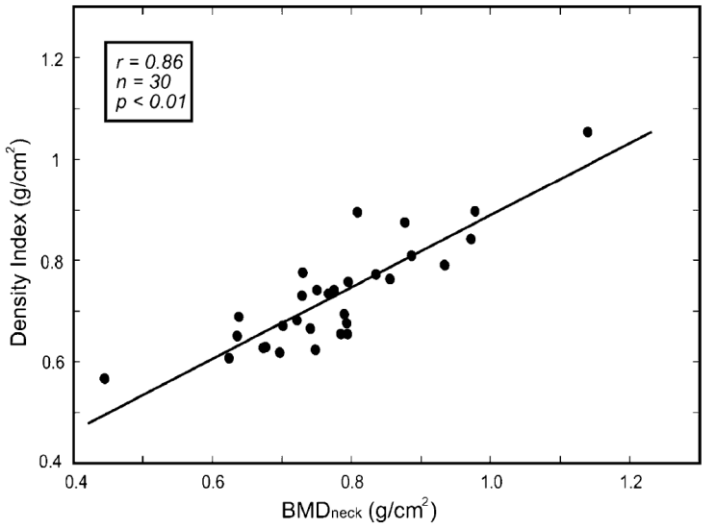
- Can QUS be used to diagnose osteoporosis according to the WHO classification? – No
- However, thresholds could be defined to identify patients at high or low risk of having osteoporosis, as follows . . .
  - Upper threshold with 90% sensitivity for identifying patients with very low likelihood of having DXA T-score diagnosis of osteoporosis (10% false negative)
  - Lower threshold with 90% specificity for identifying patients with very high likelihood of having DXA T-score diagnosis (10% false positive)
- When DXA availability is limited, DXA might be recommended for patients between the thresholds for whom the diagnosis is uncertain
- When DXA is not available, treatment might be considered when QUS measurement it at or below the lower threshold and treatment might be avoided when at or above the upper threshold

Note: This is a pre-FRAX publication.

Krieg M-A et al. J Clin Densitom. 2008;11:163-187.

PEUS Correlation, Thresholds, FRAX

30 Finnish women, mean age 74



- Threshold analysis
  - 448 Finnish women, mean age 69
  - Proximal tibia DI and T-scores at TH and FN
  - Upper threshold: 0.884 (90% sensitivity)
    - ≥ = very unlikely to have osteoporosis
  - Lower threshold: 0.779 (90% specificity)
    - ≤ = very likely to have osteoporosis
- Treatment analysis
  - UK NOGG guidelines: DXA advised for women with intermediate risk by FRAX
  - FRAX standard: 57% met criteria for DXA
  - FRAX with PEUS: 16% required DXA
- Note: Finnish subjects using GE Lunar DXA

Karjalainen JP et al. Osteoporos Int. 2012;23:1287-1295.

Karjalainen JP et al. Osteoporos Int. 2016;27:971-977.

Proximal Tibia DI and Hip T-score

Minnesota

- 555 postmenopausal women (mostly Caucasian) age 50-89
- Proximal tibia DI (average of 5 measures) detected hip osteoporosis (T-score ≤ -2.5 at FN or TH) with 80% sensitivity and 82% specificity
- DI > 0.844 upper threshold in 38%: DXA might have been avoided if PEUS had been used for pre-screening
- DI < 0.779 lower threshold in 32%
- DI association with hip T-score was weaker with BMI > 30 [soft tissue thickness over tibia does not influence PEUS measurement]
- Precision: CV 1.6%, 3.4% (2 staff)

Schousboe JT et al. Osteoporos Int. 2017;28:85-93.

New Mexico

- 293 postmenopausal women (153 Caucasian, 140 Hispanic) age ≥ 50
- Proximal tibia DI (average of 5 measures) detected hip osteoporosis (T-score ≤ -2.5 at FN or TH) with 80% sensitivity and 86% specificity for Caucasians and 80%/91% for Hispanics
- Similar performance of PEUS in US Caucasians and Hispanics, suggesting same DI thresholds can be used for both
- 31% of combined groups were between DI thresholds of 0.844 and 0.779
- Precision: CV 1.8%, 2.0% (2 staff)
- Note: USA subjects and Hologic DXA for both

Lewiecki EM. J Clin Densitom. 2021;24:175-182.

PEUS Printout

https://www.bindex.fi/en/use/

PEUS Potential Clinical Applications

- When DXA availability is limited or restricted according to national guidelines
  - Consider treatment when DI is ≤ lower threshold
  - Consider treatment according to FRAX with DI
  - Consider no treatment when DI is ≥ upper threshold
  - Consider DXA when DI is between upper and lower thresholds and FRAX shows intermediate level of risk
- When DXA is not available, consider PEUS as a substitute
  - Consider treatment when DI is ≤ lower threshold
  - Consider using DI as stand-in for FN BMD with FRAX and make treatment decisions accordingly
- Not known whether PEUS can be used to monitor treatment

Radiofrequency Echographic Multi-Spectrometry (REMS)

REMS Device

EchoS. Echolight S.P.A., Leese, Italy

- Portable device using non-invasive ultrasound technology with transducer frequency 3.5 Mhz
- Software automatically eliminates calcifications, osteophytes, and other artifacts
- Generates REMS BMD, T-scores, and Z-scores for the spine and hip that are highly correlated with DXA values
- Uses proprietary reference data of ultrasound spectral models for REMS BMD and NHANES reference data for T-scores and Z-scores

Image from https://www.medicalexpo.com/prod/echolight/product-101193-741611.html

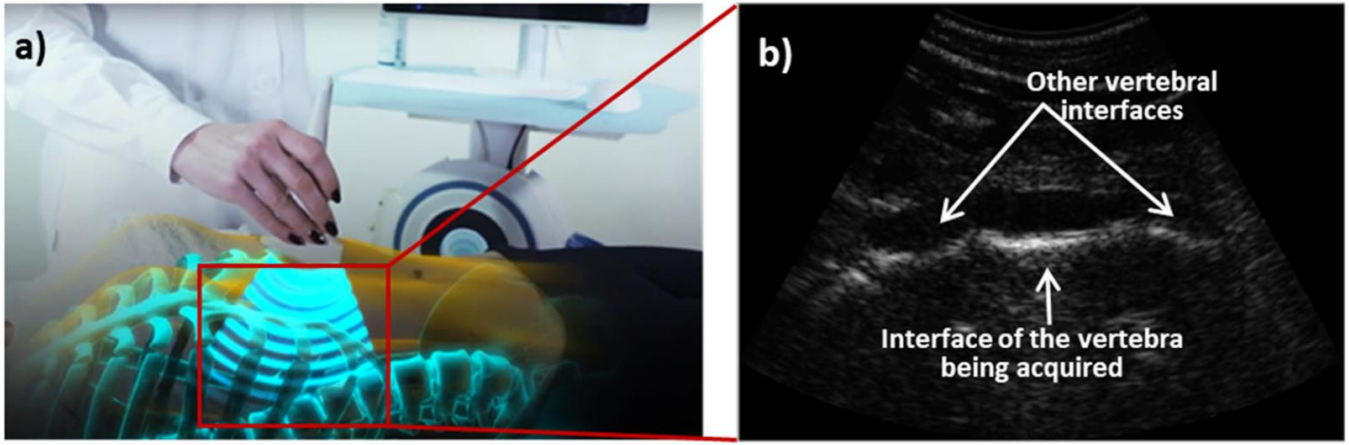
REMS Measurements at Spine and Hip

Lumbar Spine

Femoral Neck

https://www.startupbusiness.it/echolight-soluzione-medtech-per-la-diagnosi-dellosteoporosi/96672/

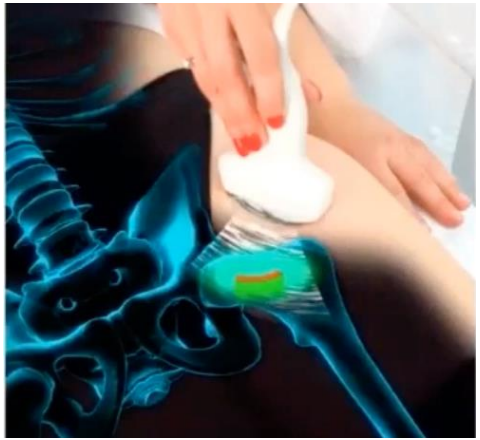
Lumbar Spine REMS

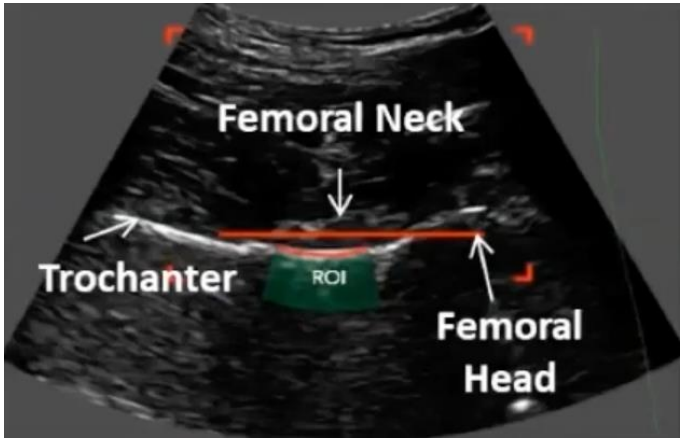


- Transducer is placed under the sternum to visualize L1, then moved down to L4 with visual and audio guidance
- Total scan time 80 sec
- Followed by automatic processing time of about 1-2 minutes

Casciaro S et al. Clin Cases Miner Bone Metab. 2015;12:142-150.

Femoral Neck REMS

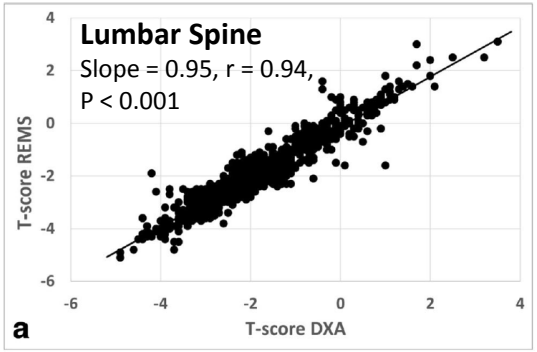


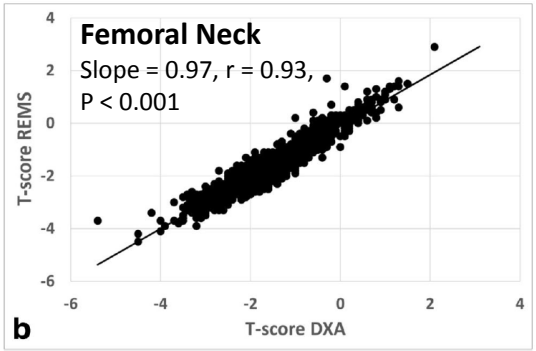


- Transducer is placed parallel to the femoral head-neck axis with visual and audio guidance
- Total scan time 40 sec
- Followed by automatic processing time of about 1 minute

https://www.youtube.com/watch?v=JYoPyR0U2T0

REMS Validation with DXA



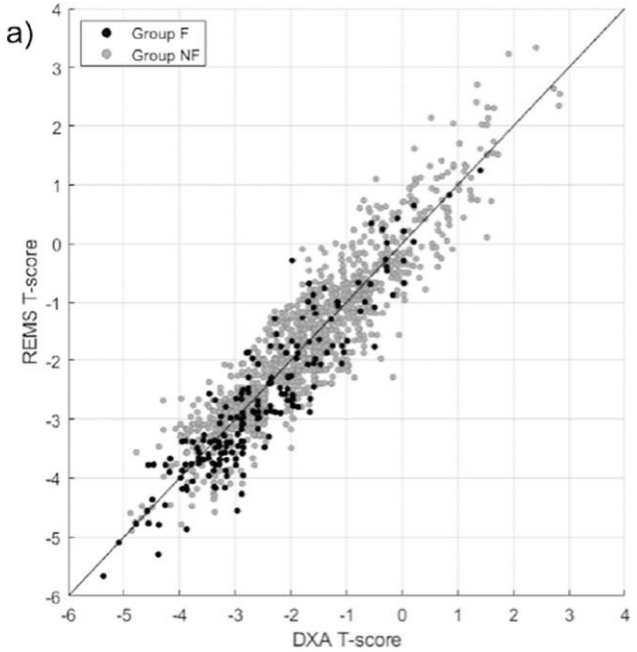


- 1914 postmenopausal women age 51-70 in Italy (1)
- 4307 women age 30-90 in Italy, Belgium, UK, and Spain (2)
- High correlation between REMS and DXA for BMD and T-scores (1, left)
- Sensitivity and specificity of REMS to discriminate patients with and without osteoporosis was > 90% at LS and FN

REMS (1)	Precision	LSC
LS	0.38%	1.05%
FN	0.32%	0.88%

1. Di Paola M et al. Osteoporos Int. 2019;30:391-402.
2. Cortet B et al. Bone. 2021;143:115786.

REMS T-score Predicts Fracture Risk



Scatterplot of Vertebral REMS and DXA T-scores in Women with and Without incident Fractures

- 5-year prospective observational study in 1516 Italian women age 30-90
- Evaluation of REMS and DXA T-scores to discriminate women who fractured or did not fracture over 5 years
- 14% fracture incidence
  - 74.5% had REMS T-score ≤ -2.5
  - 64.5% had DXA T-score ≤ -2.5
- Fragility Score: TBS-like feature to assess bone quality and predict fracture risk independently of BMD

Adami G et al. Bone. 2020;134:115297.

REMS Printouts

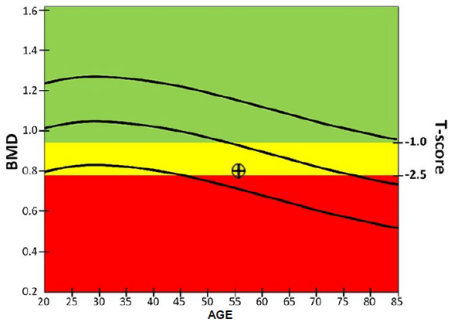
ECHOLIGHT DIAGNOSTIC CENTER
O.U. Lecce

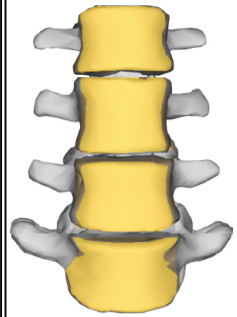
Exam date: 15/06/2020 17:34:49

Family Name: OSTEOPENIC Name: PATIENT MENOPAUSE AGE: 50

Date of Birth: 02/06/1964 Age: 56y Gender: F Weight: 60 kg H: 158 cm BMI: 24.03 kg/m²

REMS densitometry: SPINE





	BMD g/cm²	T-score	Z-score	Diagnosis
Total	0.808	-2.2	-1	Osteopenia

	BMD	T-SCORE
L1	0.679	-2.2
L2	0.782	-2.2
L3	0.846	-2.2
L4	0.884	-2.1

Fracture Risk Assessment

Fragility Score - Spine	28.5/100
5-year Risk of Major Osteoporotic Fracture	10-20‰

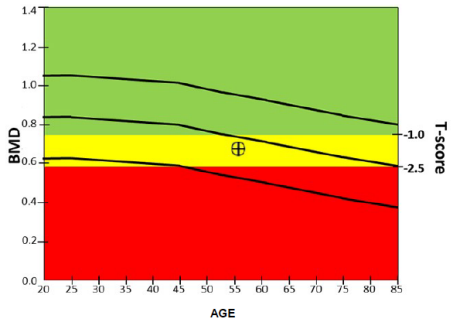
ECHOLIGHT DIAGNOSTIC CENTER
O.U. Lecce

Exam date: 15/06/2020 17:31:55

Family Name: OSTEOPENIC Name: PATIENT MENOPAUSE AGE: 50

Date of Birth: 02/06/1964 Age: 56y Gender: F Weight: 60 kg H: 158 cm BMI: 24.03 kg/m²

REMS densitometry: LEFT FEMUR



	BMD g/cm²	T-score	Z-score	Diagnosis
Neck	0.669	-1.6	-0.5	Osteopenia

	BMD	T-Score	Z-Score
Total	0.827	-0.9	-0.2
Trochanter	0.853	-0.6	0.0

Fracture Risk Assessment

Fragility Score - Hip	18.2/100
5-year Risk of Hip Fracture	4-8‰

REMS Potential Clinical Applications

- Population screening
- Patients with osteoarthritis and artifacts
- Pregnant women and children
- Short-term monitoring
- Fragility Score to assess bone quality
- Evaluation of cartilage and muscle mass

Impact Microindentation (IMI)

Formerly known as

Reference Point Indentation (RPI)

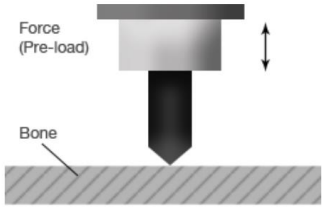
IMI Device: Clinical

OsteoProbe. Active Life Scientific, Santa Barbara, CA

- Novel technique for measuring tissue-level material properties of cortical bone
- Two devices
  - Osteoprobe: used in living humans with handheld device that generates a single high force load of 40 N over 0.25 msec (impact microindentation - IMI)
  - BioDent: used in animals with cyclic low force loading and unloading of 0-10 N over several sec (cyclic reference point microindentation- CMI)
- Known force is applied
- Depth of penetration in the outer cortex is measured
- Output is Bone Material Strength index (BMSi)

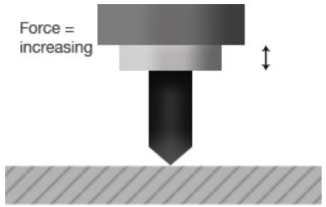
http://research.activelifescientific.com/osteoprobe/

Diez-Perez A et al. Bone Reports. 2016;5:181-185.



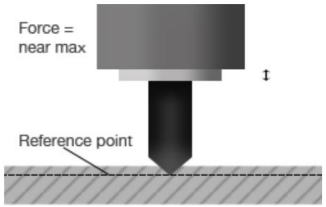
Step 1

The tip assembly is inserted through any soft tissue to the cortical bone surface.



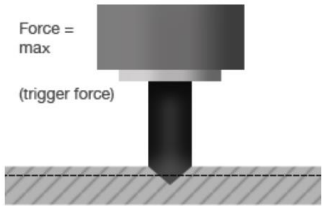
Step 2

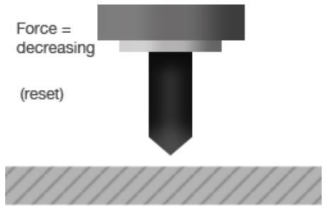
The user compresses the outer housing, pressing the tip lightly into the cortical bone surface.

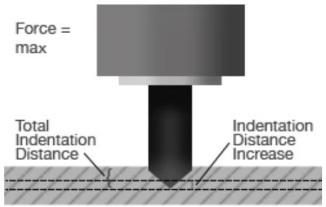


Step 3

At maximum compression (~10N), the tip is pressed into the bone surface enough to set a reference point.

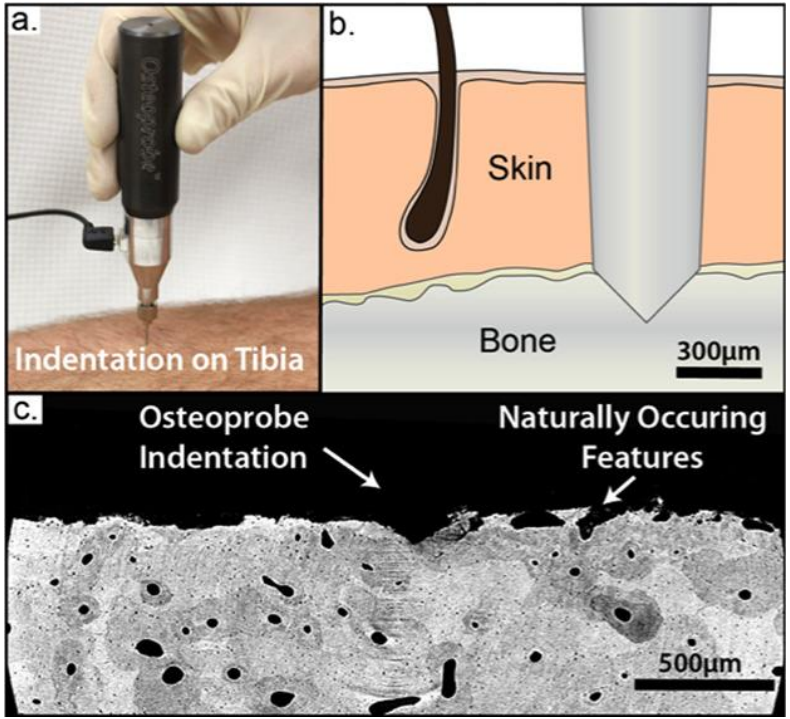






http://research.activelifescientific.com/how-does-osteoprobe-work/

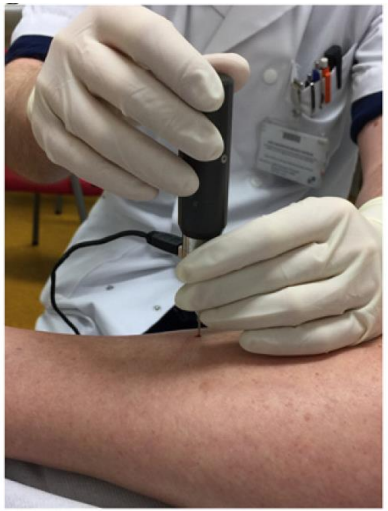
Microindentation is Very Small



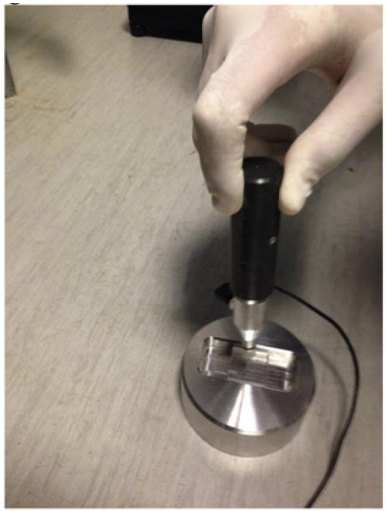
https://asbmr.onlinelibrary.wiley.com/doi/full/10.1002/jbmr.2497

IMI Procedure

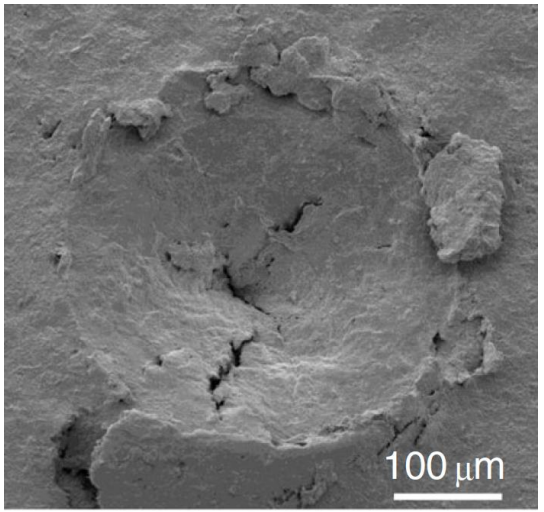
Local Anesthetic



8-10 Indentations (at least 5 must be valid)



8 Indentations of BMSi Reference Material

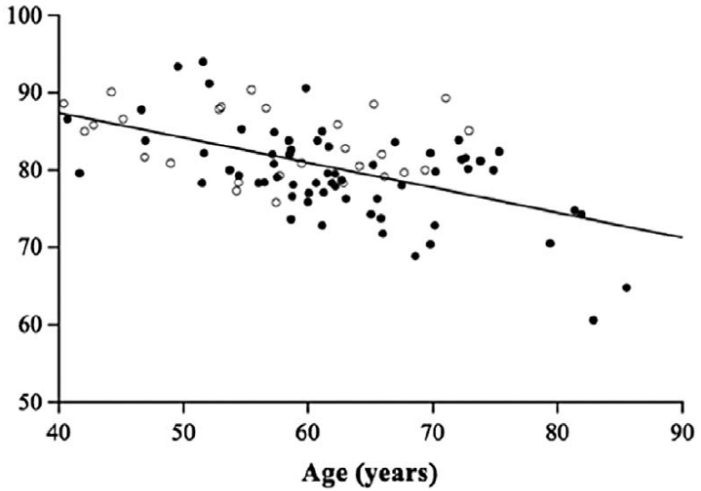


Scanning Electron Microscopy of IMI Indent

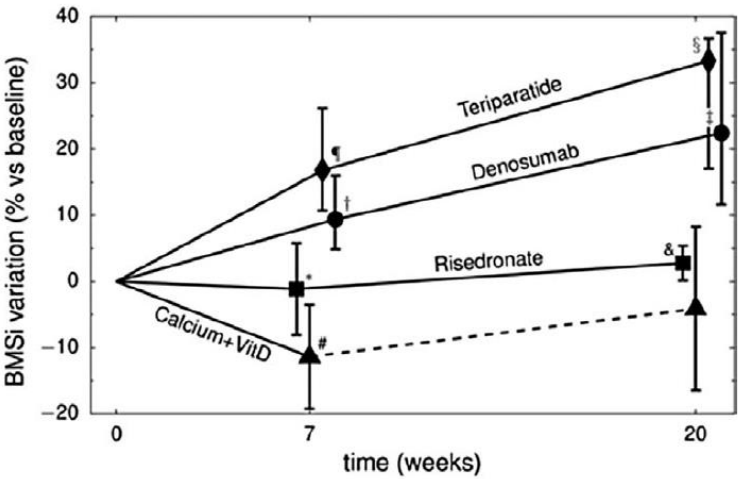
Diez-Perez A et al. Bone Reports. 2016;5:181-185.

BMSi Clinical Correlations

BMSi Declines with Advancing Age

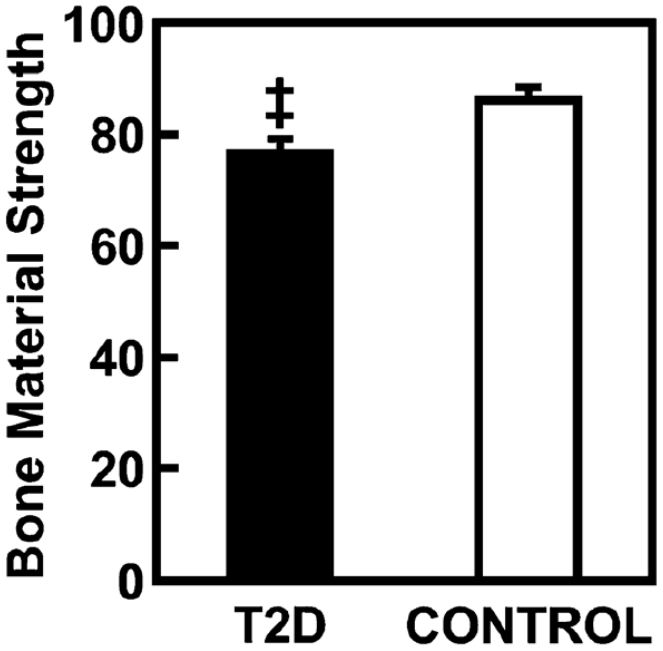


BMSi Increases with Some Medications



Allen MR et al. J Bone Miner Res. 2015; 30:1539-1550.

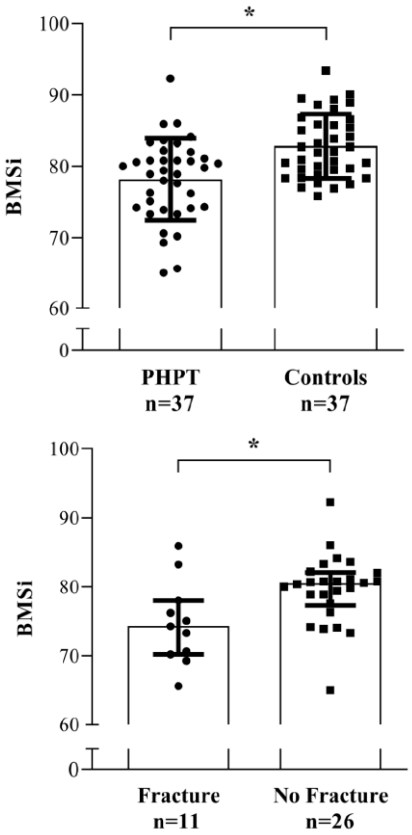
Lower BMSi with Type 2 Diabetes



- IMI in 30 postmenopausal women age 50-80 with T2D for > 10 years and 30 non-diabetic age-matched controls (1)
- BMSi was significantly lower in diabetics (-11.7%; $P < 0.001$) compared with non-diabetics (left, unadjusted) and when adjusted for BMI, age, hypertension, nephropathy, neuropathy, retinopathy, and vascular disease
- Diabetics also lower BTMs ($P < 0.001$) and tended to have greater cortical porosity at the distal radius with HRpQCT (NS)
- In another study of men with T2D compared with non-diabetic controls, BMSi and TBS were lower than controls despite no difference in BMD (2)

1. Farr JN et al. J Bone Miner Res. 2014;29:784-786.
2. Holloway-Kew AL et al. Bone 2021;142:115685.

Lower BMSi in Women with PHPT



- Cross-sectional study of 37 women with PHPT, including 11 with fragility fractures, compared with 37 women controls who were euparathyroid matched for age and fragility fracture status
- BMSi was significantly lower in women with PHPT than controls ($P < 0.001$), despite no difference in BMD at LS and FN
- BMSi was significantly lower in the 11 PHPT patients with fractures vs the 26 PHPT patients without fractures ($P = 0.015$), with lower FN BMD and similar LS BMD in fracture patients

Schoeb M et al. J Clin Endocrinol Metab. 2021;Mar 29;dgab207.

IMI Potential Applications

- Research
  - Better understanding of the contribution of bone material properties to bone strength, independent of BMD
- Clinical
  - Assessment of bone strength for patients with discrepancies between BMD and fracture risk, such as those with T2D, PHPT, glucocorticoids, stress fractures, normal BMD and low trauma fractures, normal BMD and “soft bones” with orthopedic surgery
  - Complementary to conventional methods, not a replacement

FDA Approval vs. Clearance of Devices

Class III Devices are Approved

- Class III devices are ones that are implanted or may pose high risk (e.g., pacemakers, artificial heart valves)
- Manufacturer submits application and results of clinical testing
- FDA approval means the benefits of the product outweigh the known risks for the intended use

Class I and II Devices are Cleared

- Class I (low risk – electric toothbrush) and II (moderate risk – diagnostic ultrasound) devices are used externally are are considered safer than class III devices when use as intended
- Manufacturer submits premarket notification submission or 510(k)
- FDA clearance means the manufacturer has demonstrated that the product is substantially equivalent to another legally marketed device (“predicate device”) that already has FDA clearance or approval
- Once cleared, the device may be marketed and sold in the US

Regulatory

- Bindex PEUS device
  - Europe: approved for clinical use
  - US: FDA cleared, AMA CPT category III code 0508T [temporary code for emerging technologies], CMS approved coverage in the Ambulatory Surgical Center (ASC) setting
- EchoS REMS device
  - Europe: approved for clinical use
  - US: FDA cleared, unclassified ultrasound code 76999 has been used
- Osteoprobe IMI device
  - Europe: approved for clinical use
  - US: investigational

From websites of device manufacturers and contact with representatives

BEYOND BMD

DR. IRINEL STANCIU, MD, FACE, CCD, ECNU

FEEL BETTER. DO MORE.

PANORAMA
Orthopedics & Spine Center

DISCLOSURES:

PANORAMA
Orthopedics & Spine Center
FEEL BETTER. DO MORE.

- Member of speaker bureau for Radius Health and Alexion Pharmaceuticals
- Scientific advisory board for Ultragenyx
- Principal investigator for research trials with Radius and Ultragenyx (research funds received by Panorama)

OBJECTIVES

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- Describe technology and clinical applications of the Trabecular Bone Score (TBS)
- Describe the technology and clinical applications of the Biomechanical Computed Tomography (BCT)
- Describe the technology and clinical applications of the HRpQCT

OSTEOPOROSIS = LOW BONE MASS AND MICROARCHITECTURE DETERIORATION

PANORAMA
Orthopedics & Spine Center
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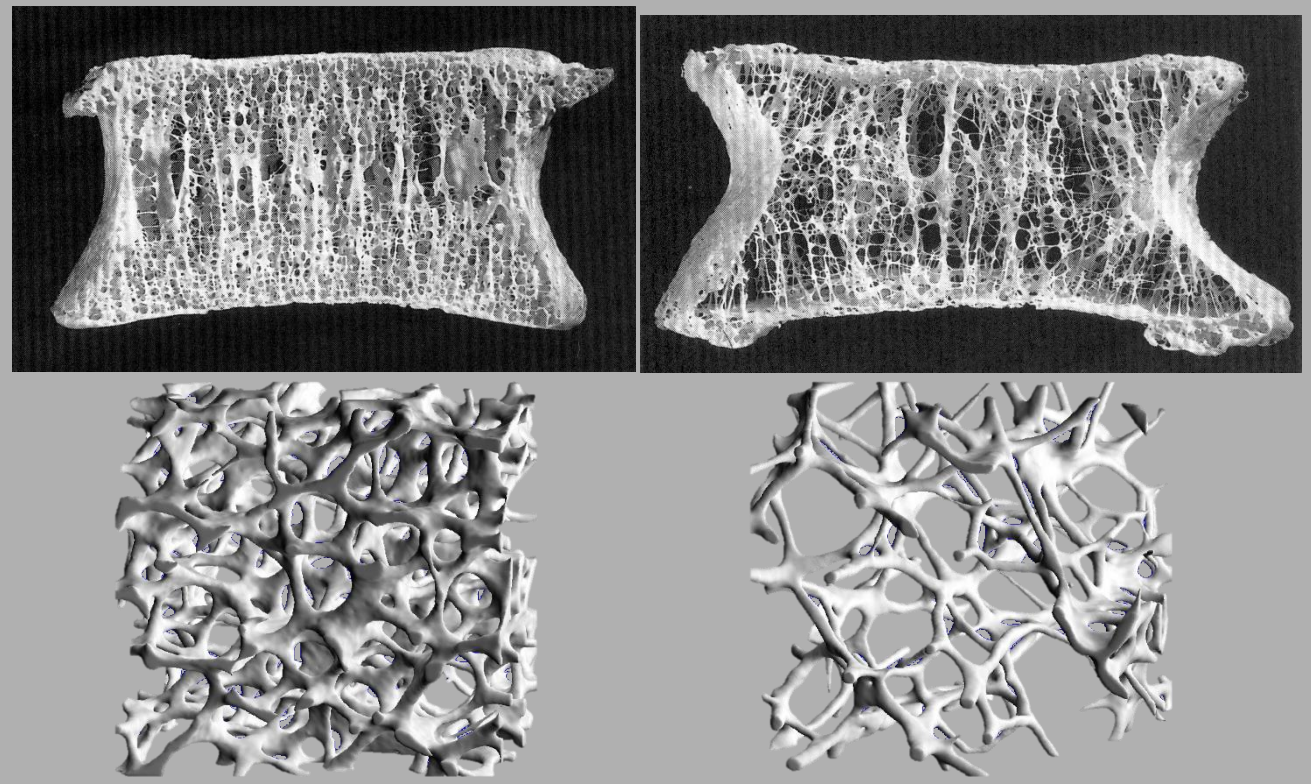
"A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture."



*Consensus Development Conference: Diagnosis, Prophylaxis, and Treatment of Osteoporosis. Am J Med. 1991;90:107- d

BONE STRENGTH

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BONE DENSITY

BONE QUALITY

- BONE TURNOVER
- BONE REMODELING
- BONE GEOMETRY
- MICROARCHITECTURE
- MINERALIZATION
- MICRODAMAGE
- MATRIX AND MINERAL COMPOSITION

TRABECULAR BONE SCORE
A NEW *BONE STRUCTURE* ASSESSMENT TECHNIQUE ENHANCES IDENTIFICATION OF FRACTURE RISK

Discerns differences between DXA scans that show similar BMD measurements

White Paper by Medimaps

1631 results on PubMed (English, Humans)

WHAT IS TRABECULAR BONE SCORE (TBS)?

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- Is a DXA software program that estimates bone texture information from the 2D LS DXA scan
  - Is a derived unitless index, not a direct physical measure
- TBS - highly correlated evaluation of trabecular microarchitecture and fracture risk
- TBS provides fracture risk information that is additive to BMD and clinical risk factors

Silva et al. J Bone Miner Res. 2014 29:518–530 and White paper by Medimaps

DIFFERENT BONE TEXTURE (TBS) DESPITE SAME L1-L4 BMD

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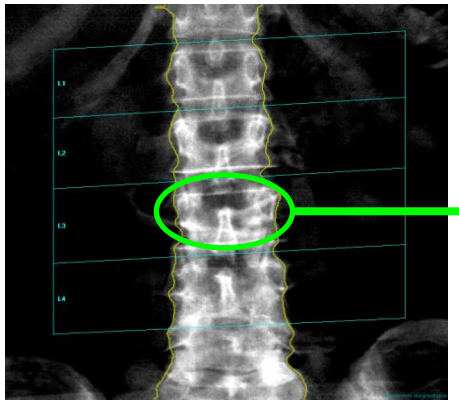
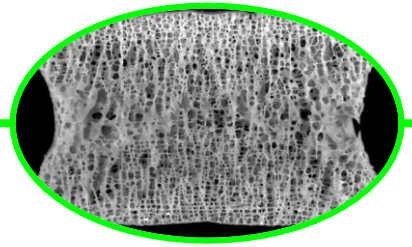
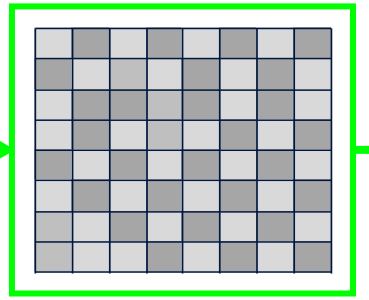
Two patients with
Same L1-L4 BMD



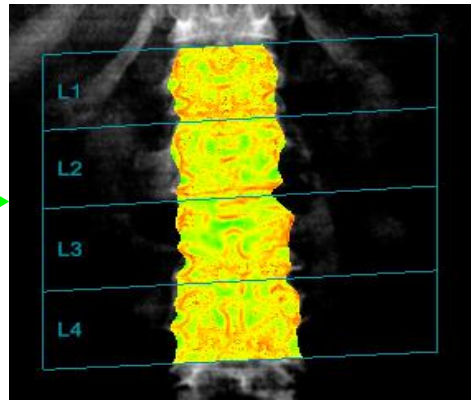
Normal trabecular
Bone architecture

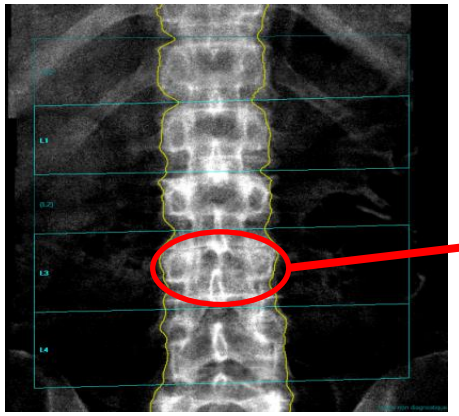




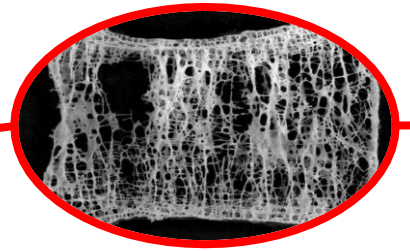
Homogeneous:
High TBS

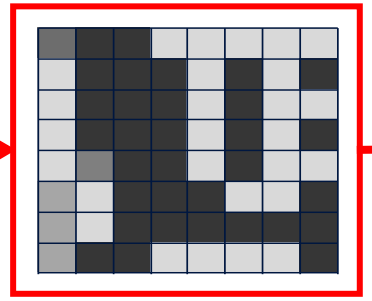
TBS L1-L4: 1.457



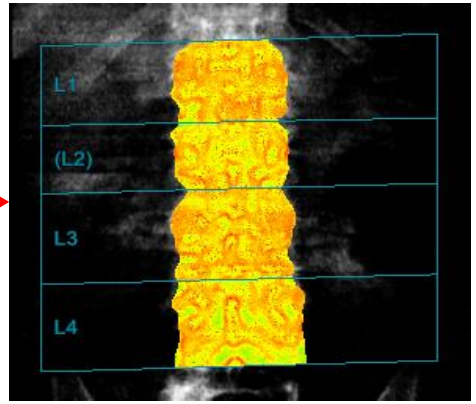


Degraded trabecular
bone architecture



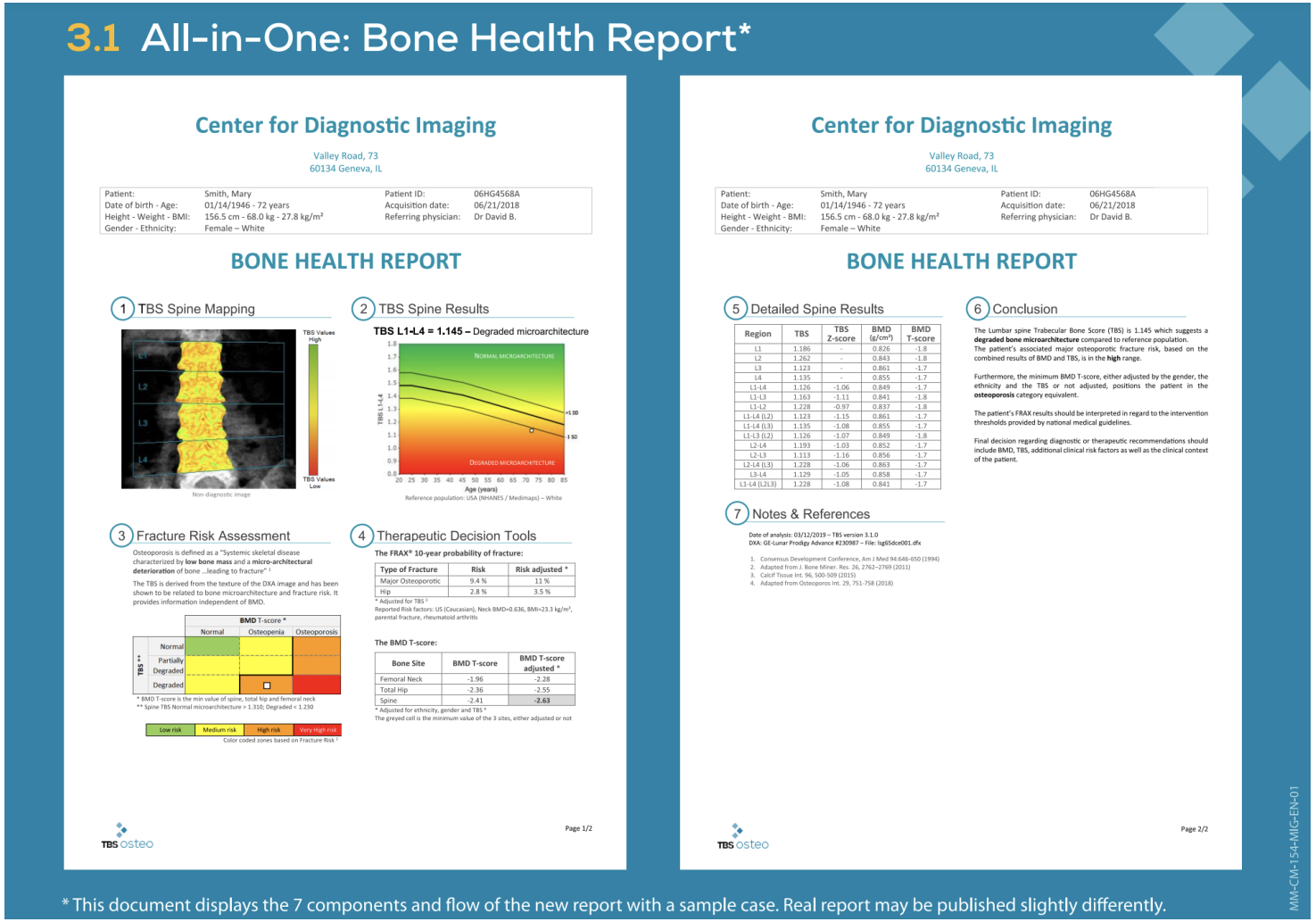


Heterogeneous:
Low TBS

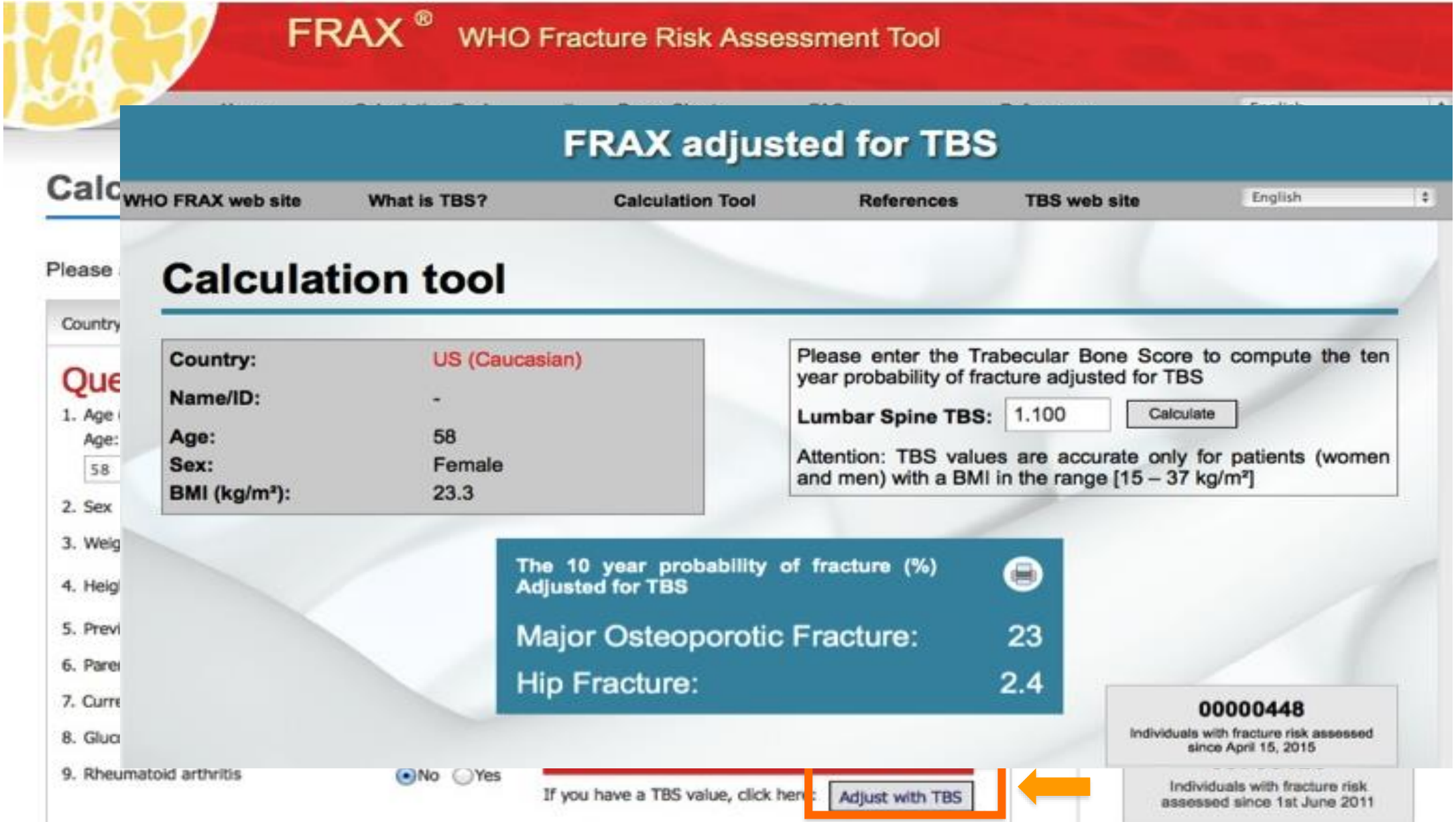


TRABECULAR BONE SCORE (TBS) REPORT

- TBS iNsight software Medimaps Group Geneva, Switzerland
- TBS report is obtained by one click
- Provides an indirect assessment of trabecular microarchitecture that is an independent predictor of fracture risk.



TBS Data Can be Used to Adjust FRAX



TBS IS FDA APPROVED AND RECOMMENDED BY ISCD

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"Med-Imaps TBS iNsight is a software provided for use as a complement to a DXA analysis. … TBS is derived from the texture of the [AP spine] DXA image and has been shown to be related to bone microarchitecture and fracture risk … independent of BMD…"

2015 ISCD Position Development Conference

Fracture Risk Prediction by Non-BMD DXA Measures: the 2015 ISCD Official Positions Part 2: Trabecular Bone Score

Barbara C. Silva,[,1] Susan B. Broy,[2] Stephanie Boutroy,[3] John T. Schousboe,[4] John A. Shepherd,[5] and William D. Leslie[6,7]*

TRABECULAR BONE SCORE (TBS)
2019 ISCD POSITIONS

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- TBS is associated with vertebral, hip and major osteoporotic fracture risk in **postmenopausal women**.
- TBS is associated with **major osteoporotic fracture risk in postmenopausal women with type II diabetes**.
- TBS is associated with major osteoporotic fracture and hip fracture risk in **men over the age of 50 years**.
- TBS **should not be used alone** to determine treatment recommendations in clinical practice.
- TBS can be used in association with FRAX and BMD to adjust FRAX-probability of fracture in postmenopausal women and older men.
- In patients receiving anti-fracture therapy:
  - The role of TBS in monitoring anti-resorptive therapy is unclear.
  - TBS is **potentially useful** for monitoring anabolic therapy.

ISCD
The International Society
For Clinical Densitometry

Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. 22, no. 4, 501–505, 2019

1094-6950/22:501–505/$36.00
https://doi.org/10.1016/j.jocd.2019.07.006

2019 ISCD Official Position

Dual-energy X-ray Absorptiometry Monitoring with Trabecular Bone Score: 2019 ISCD Official Position

Kelly Krohn,[1] Elliott N. Schwartz,[2] Yoon-Sok Chung,[3] and E. Michael Lewiecki[4,*]

[1] Department of Orthopedic Surgery, University of Arizona College of Medicine Phoenix, AZ, USA; [2] Northern California Institute For Bone Health, Orinda, CA, USA; [3] Ajou University School of Medicine, Suwon, South Korea; and [4] New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA

KEY QUESTIONS

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- 1. Is TBS useful to monitor patients treated with **antiresorptive agents?**

- 2. Is TBS useful to monitor patients treated with **teriparatide and abaloparatide?**

TBS PRECISION

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- The least significant change (LSC) for TBS can be estimated to be about **5.8% (3.1-5.8% in published data**) or calculated by a dual-energy X-ray absorptiometry facility using the same methodology that is used for bone mineral density (BMD) precision assessment to calculate BMD LSC.
- TBS precision is better when LS BMD precision is better - TBS LSC may be at the low end of this range at a facility with very low LS BMD LSC
- A significant decrease of TBS on treatment may represent a poor response to treatment and increasing fracture risk.

KEY QUESTIONS AND ANSWERS

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1. Is TBS useful to monitor patients treated with **antiresorptive agents?**
   - TBS **does not** appear to be clinically useful to monitor the skeletal effects of **bisphosphonates and denosumab (unclear role)**
2. Is TBS useful to monitor patients treated with **teriparatide and abaloparatide?**
   - TBS is **potentially useful** as a component of monitoring the skeletal effects of **teriparatide and abaloparatide**.

PHYSICAL AND LIFESTYLE FACTORS ASSOCIATED WITH TRABECULAR BONE SCORE VALUES

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- Cross-sectional study, 894 M and 682 F (24–98 years) enrolled in the Geelong Osteoporosis Study.
  - TBS was assessed by analysis of lumbar spine DXA scans (Lunar Prodigy) using TBS iNsight software (Version 2.2).
  - Bivariate and multivariable linear regression models
- Low mobility and the use of antiresorptive medication were associated with **lower TBS in both men and women.**
- Low childhood physical activity was associated with **lower TBS in men**.
- Prior fracture, use of glucocorticosteroids, and total calcium intake were also associated with **lower TBS in women**.

Anderson KB, Holloway-Kew KL, Hans D, Kotowicz MA, Hyde NK, Pasco JA. Physical and lifestyle factors associated with trabecular bone score values. Arch Osteoporos. 2020;15(1):177.

CLINICAL RISK FACTORS ASSOCIATED WITH TBS

Clinical factors associated with higher TBS	Clinical factors associated with lower TBS
Non-Hispanic white ethnicity (women)	Older age
Recent osteoporosis therapy	Non-Hispanic black and Mexican-American ethnicity (women)
Higher BMD (spine or hip)	Recent glucocorticoid use
	Prior major fracture
	Type 2 diabetes
	Rheumatoid arthritis
	Chronic obstructive pulmonary disease
	High alcohol intake
	Renal transplantation
	Higher BMI and other measures of body size (weight, waist circumference, total body fat mass, trunk fat and lean mass)[a]

BMD, bone mineral density; TBS, trabecular bone score.
[a]Dual-energy absorptiometry scanner and trabecular bone score software version dependent.

Martineau, Patrick, , et al. "Utility of trabecular bone score in the evaluation of osteoporosis". Current Opinion in Endocrinology & Diabetes and Obesity, vol. 24, no. 6, December 2017, pp. 402–410.

TBS HAS PARTICULAR ADVANTAGES OVER BMD FOR SPECIFIC CAUSES OF INCREASED FRACTURE RISK

- chronic corticosteroid use
- type-2 diabetes
- chronic kidney disease
- primary hyperparathyroidism
- patients being treated with aromatase inhibitors

D. Hans, E. Šteňová, and O. Lamy, "The Trabecular Bone Score (TBS) Complements DXA and the FRAX as a Fracture Risk Assessment Tool in Routine Clinical Practice," Curr. Osteoporos. Rep., Oct. 2017.
E. Shevroja, O. Lamy, L. Kohlmeier, F. Koromani, F. Rivadeneira, and D. Hans, "Use of Trabecular Bone Score (TBS) as a Complementary Approach to Dual-energy," J. Clin. Densitom. Off. J. Int. Soc. Clin. Densitom., vol. 20, no. 3, pp. 334–345, Sep. 2017

BIOMECHANICAL CT (BCT)

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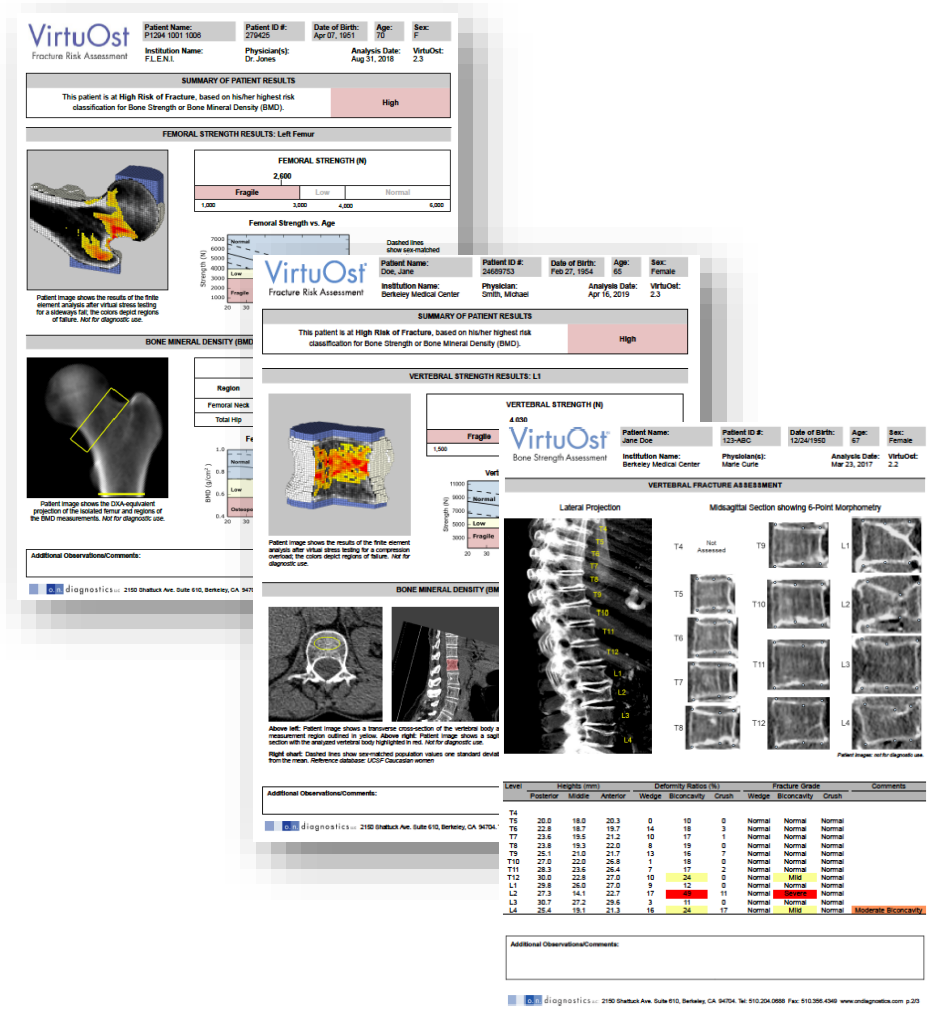
- Quantitative computed tomography (QCT) uses conventional CT imaging of the lumbar vertebrae and proximal femur, concurrently with phantoms with known volumetric BMD values to convert image contrast into quantitative measures of volumetric BMD
- QCT does not provide the resolution necessary to evaluate trabeculae.
- Finite element analysis (FEA) is a computer modeling technique that, when coupled with QCT, provides a non-invasive approach to estimate bone strength
- QCT-based FEA extends interpretations of QCT to evaluate whole bone structure and shape as well as estimating the bone strength

THE BIOMECHANICAL (BCT) CT

A fully reimbursed, zero radiation, patient-convenient, diagnostic service* for bone fragility

- Can utilize previously-acquired CT* scans taken for any medical indication — no need for a separate patient procedure
- Can include VFA analysis to detect existing vertebral fractures
- Offer to all CT patients w/o a recent DXA
- Well suited for pre-operative bone quality evaluation for ortho surgery patients



*** Send hip- or spine-containing CT scan to OND; OND performs its VirtuOst BCT test and returns results**

VirtuOst® BCT is Extensively Validated

Validated in > 7,000 patients, > 40 peer-reviewed journal articles

Osteoporosis International (2020) 31:1025–1048
https://doi.org/10.1007/s00198-020-05384-2

REVIEW

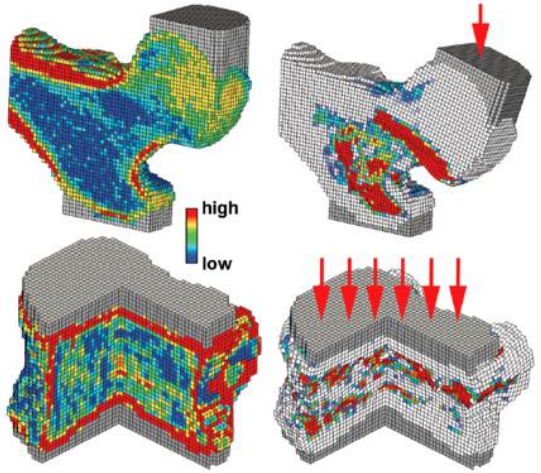
Check for updates

Biomechanical Computed Tomography analysis (BCT) for clinical assessment of osteoporosis

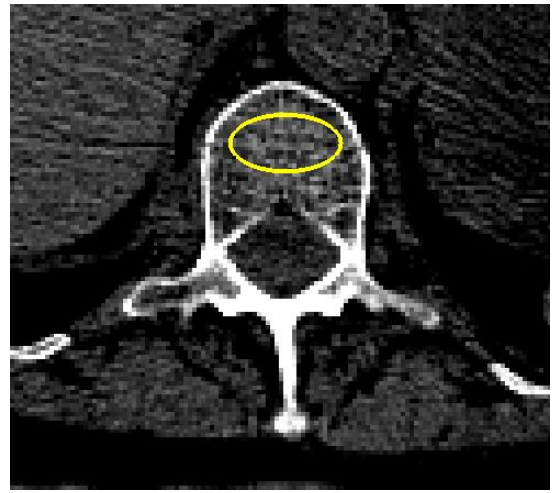
T.M. Keaveny[1] · B.L. Clarke[2] · F. Cosman[3] · E.S. Orwoll[4] · E.S. Siris[5] · S. Khosla[2] · M.L. Bouxsein[6]

"Together, this body of evidence supports BCT as an accurate and convenient diagnostic test for osteoporosis in both sexes, particularly when used opportunistically for patients already with CT."

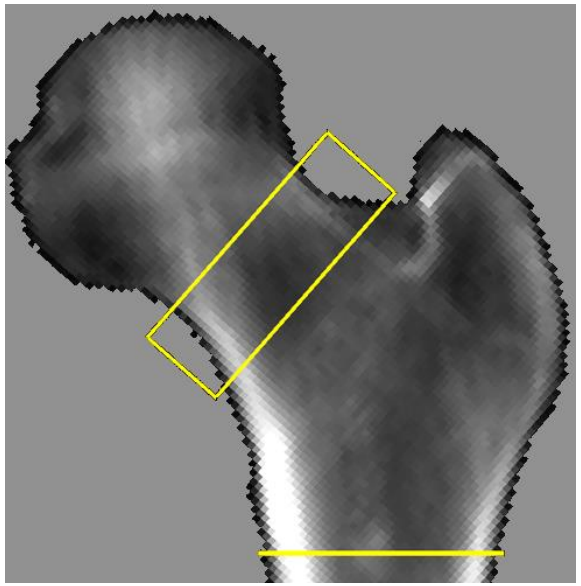
The **VirtuOst test** measures both **bone strength and BMD at the hip and/or spine,** with FDA-cleared and validated interventional thresholds to facilitate clinical interpretation and decision making.



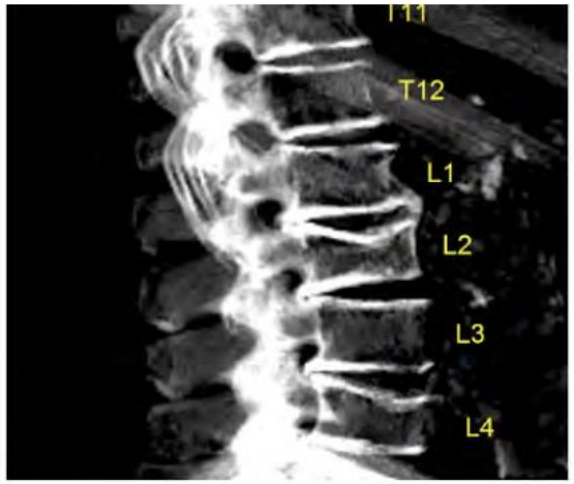
Spine BMD: VirtuOst provides a **"volumetric" trabecular BMD** at the spine, for an elliptical region of trabecular bone within the central 8–10 mm of the vertebral body. As per clinical recommendations from the *ACR* and the *ISCD*, **BMD ≤ 80 mg/cm³ indicates osteoporosis.**

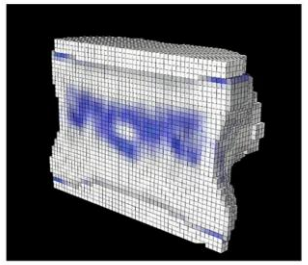


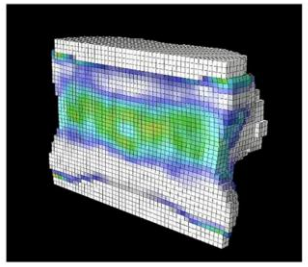
Hip BMD: VirtuOst provides **DXA-equivalent BMD T-scores for the femoral neck and total hip regions.** The T-scores utilize the NHANES III Causcasian reference database, assume the young-female reference values for both sexes, and can be used with the *FRAX® online calculator*.

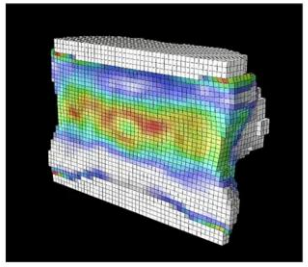


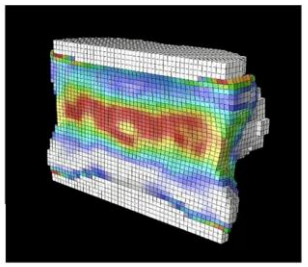
- ***VirtuOst-VFA*** identifies existing vertebral fractures









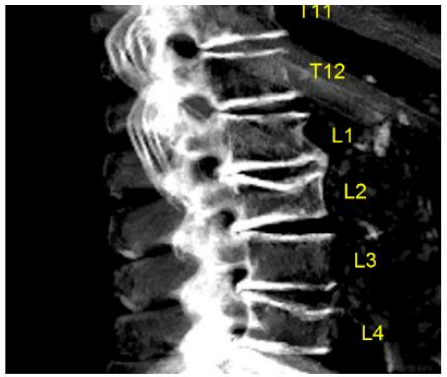


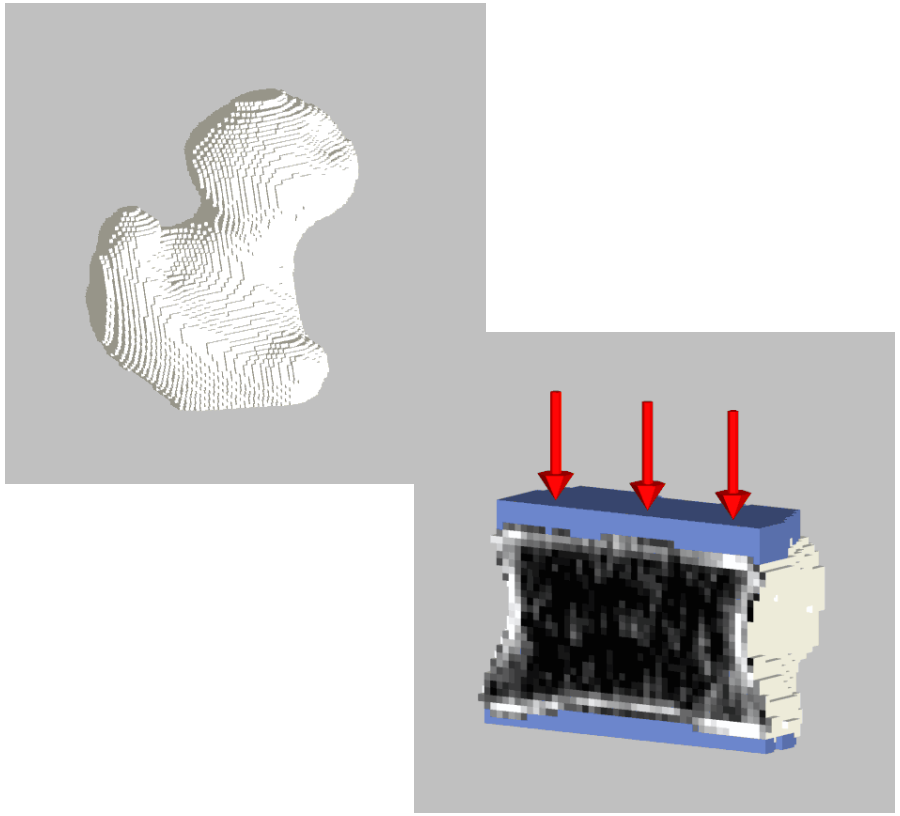
THE SCIENCE BEHIND *VIRTUOST® BCT*

"Biomechanical CT" (BCT) harnesses advanced image processing of CT scans, AI, established biomechanical principles, and engineering-based, finite element analysis

VirtuOst creates a personalized 3D model of a patient's bone and subjects it to a **virtual stress test**

VirtuOst-VFA identifies existing vertebral fractures

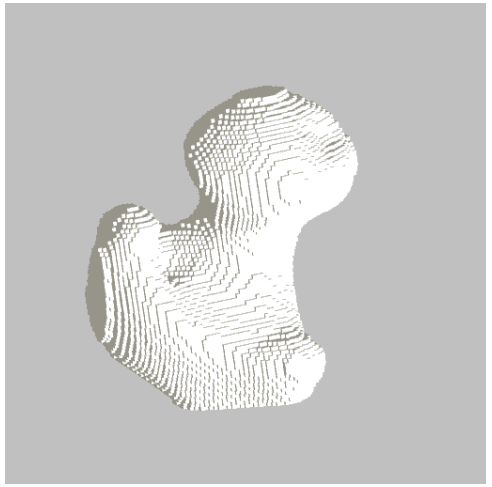




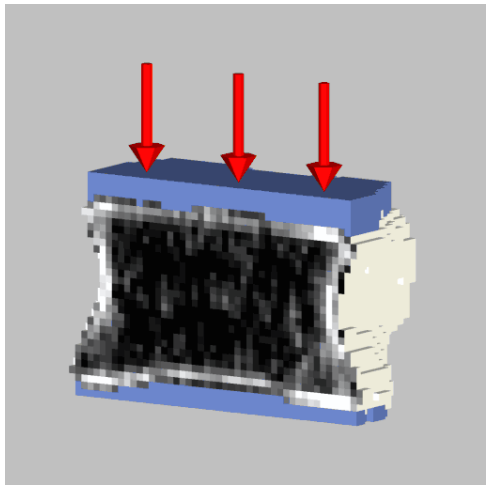
See videos at *https://ondiagnostics.com/physicians/overview/*

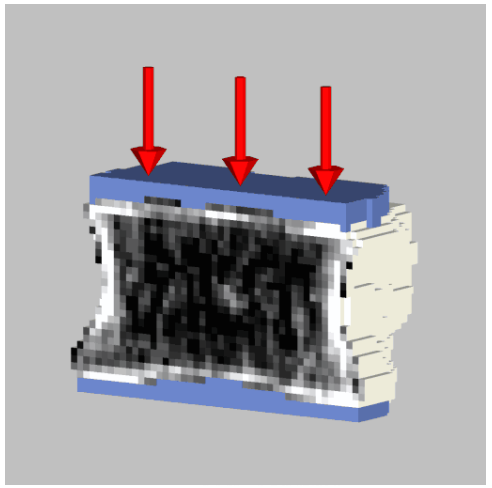
BIOMECHANICAL COMPUTED TOMOGRAPHY (BCT)

Hip



Spine





Now

After Treatment

Virtual stress testing

- Bone strength
- Bone density
- Fracture risk assessment
- Optionally also VFA (from CT)

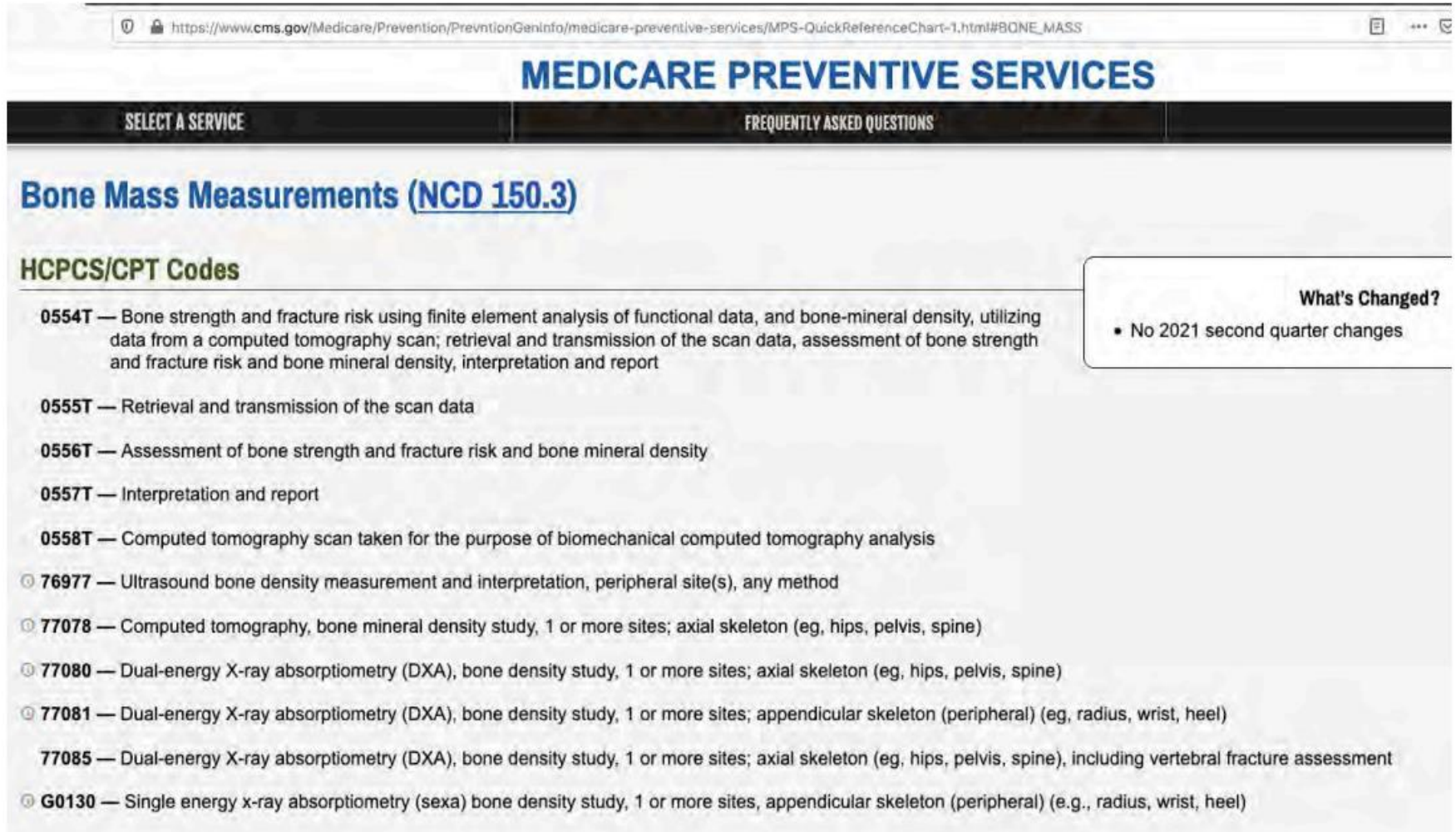
➢ Can uniquely identify some patients with osteoporosis — *compromised bone strength at high risk of fracture* — who are missed by DXA

➢ Can utilize CT scans containing the hip or lower spine, *previously taken for any medical indication*

- 8M patients/yr are BCT-eligible
- No extra patient visit needed

Animations courtesy of O.N. Diagnostics

- **BCT is now nationally covered and reimbursed as a BMM preventative services benefit**
- **Same coverage rules as for CT-bone density (diagnosis but not monitoring)**
- **BCT w/ or w/o a new CT**



https://www.cms.gov/Medicare/Prevention/PrevntionGenInfo/medicare-preventive-services/MPS-QuickReferenceChart-1.html#BONE_MASS

MEDICARE PREVENTIVE SERVICES

SELECT A SERVICE | FREQUENTLY ASKED QUESTIONS

Bone Mass Measurements (NCD 150.3)

HCPCS/CPT Codes

What's Changed?
- No 2021 second quarter changes

0554T — Bone strength and fracture risk using finite element analysis of functional data, and bone-mineral density, utilizing data from a computed tomography scan; retrieval and transmission of the scan data, assessment of bone strength and fracture risk and bone mineral density, interpretation and report

0555T — Retrieval and transmission of the scan data

0556T — Assessment of bone strength and fracture risk and bone mineral density

0557T — Interpretation and report

0558T — Computed tomography scan taken for the purpose of biomechanical computed tomography analysis

76977 — Ultrasound bone density measurement and interpretation, peripheral site(s), any method

77078 — Computed tomography, bone mineral density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine)

77080 — Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine)

77081 — Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; appendicular skeleton (peripheral) (eg, radius, wrist, heel)

77085 — Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine), including vertebral fracture assessment

G0130 — Single energy x-ray absorptiometry (sexa) bone density study, 1 or more sites, appendicular skeleton (peripheral) (e.g., radius, wrist, heel)

Logistics for BCT

- ✓ Treating physician places order if a BMM is medically necessary for the patient
- ✓ Imaging facility sends CT scan to lab [CPT code 0555T]; lab performs BCT analysis [CPT code 0556T]
- ✓ Physician interprets BCT results [CPT code 0557T] and returns medical report to treating physician

HIGH RESOLUTION PERIPHERAL COMPUTED TOMGRAPHY (HRPQCT)

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- **Non-invasive 3-D** method to evaluate compartment-specific vBMD and bone microarchitecture in the peripheral skeleton (radius and tibia) at high resolutions (60-80 μ).
- First device ~ 2005
- Basic imaging principles are based on the interaction of ionizing radiation (X-rays) with matter.
- X-ray attenuation data is acquired at multiple projections around the specimen, which allows for a 3D image to be reconstructed
- **Low radiation:** standard HR-pQCT scan at the distal radius or tibia is 3– 5 μSv depending on the scanner generation
  - hip scan using DXA ~ 9 μSv
  - standard chest X-ray ~100 μSv
  - hip CT scan ~ 286–506 μSv

Whittier DE, Boyd SK, Burghardt AJ, et al. Guidelines for the assessment of bone density and microarchitecture in vivo using high-resolution peripheral quantitative computed tomography. *Osteoporos Int*. 2020;31(9):1607-1627.

XTREME CT -SCANCO

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- **Second-generation HR-pQCT** (XtremeCT II, Scanco Medical AG, Brütisellen, Switzerland)

XtremeCT II
< 58 µm resolution, 30 s-2.1 min, < 5 uSv

- **First-generation HR-pQCT** (XtremeCT, Scanco Medical AG, Brütisellen, Switzerland) = standard

XtremeCT I
82 µm resolution, 2.6 min, < 5 uSv

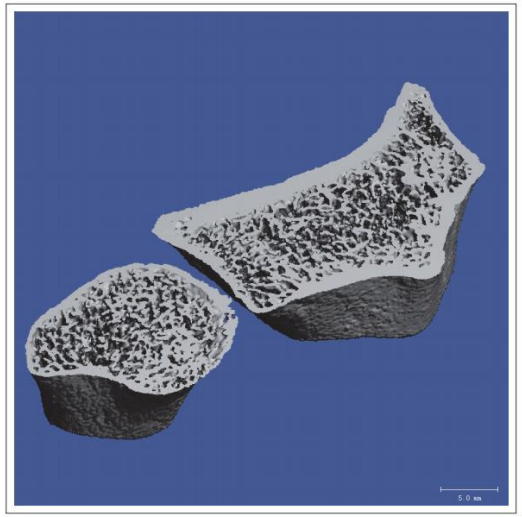
http://www.scanco.ch/en/systems-solutions/clinical-microct/xtremect I .html

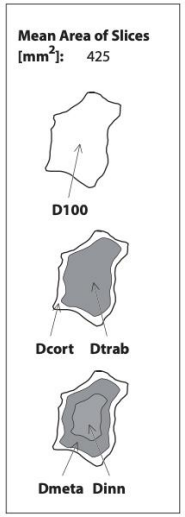
- Increased our understanding of age-related changes and sex differences in bone microarchitecture, differences in bone structure across a wide range of bone metabolic disorders, fracture risk, and the response of bone to different osteoporosis therapies.
- **Density Parameters:** Cortical and trabecular density
- **Structural Parameters:** Trabecular Thickness, Trabecular Separation, Trabecular Number, Volume Fraction, Cortical Thickness, Cortical porosity, Arterial calcification
- The decision of **which density and microarchitecture parameters** to report depends on the research question.
- Difficult to implement - at this time - in clinical practice

Cheung AM, Adachi JD, Hanley DA, et al. High-resolution peripheral quantitative computed tomography for the assessment of bone strength and structure: a review by the Canadian Bone Strength Working Group. Curr Osteoporos Rep. 2013;11(2):136-146.
Manhard MK, Nyman JS, Does MD. Advances in imaging approaches to fracture risk evaluation. Transl Res. 2017;181:1-14.

XTREME CT II - SCANCO REPORT

Site: Radius
Pat-No.: 10 Filename: C0000300
M-No.: 310 Date: 12-MAR-2017 10:31
Born: 01.01.1949 Age: 68



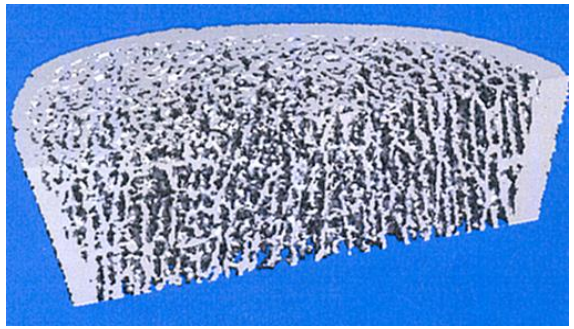


Densities			Structure		
D100	[mg HA/ccm]	283	BV/TV	[1]	0.177
Dtrab	[mg HA/ccm]	212	Tb.N	[1/mm]	2.420
Dmeta	[mg HA/ccm]	345	Tb.Th	[mm]	0.073
Dinn	[mg HA/ccm]	122	Tb.Sp	[mm]	0.340
Ratio: Meta/Inn	[1]	2.83	Tb.1/N.SD	[mm]	0.068
Dcort	[mg HA/ccm]	729	C.Th	[mm]	0.27

D100	Average Bone Density	BV/TV	Trab. Bone Volume to Tissue Volume
Dtrab	Trabecular Bone Density	Tb.N	Number of Trabeculae
Dmeta	Meta Trab. Bone Density	Tb.Th	Trabecular Thickness
Dinn	Inner Trab. Bone Density	Tb.Sp	Trabecular Separation
Meta/Inn	Ratio Meta to Inner Density	Tb.1/N.SD	StDev of 1/Tb.N: Inhomogeneity of Network
Dcort	Cortical Bone Density	C.Th	Cortical Thickness

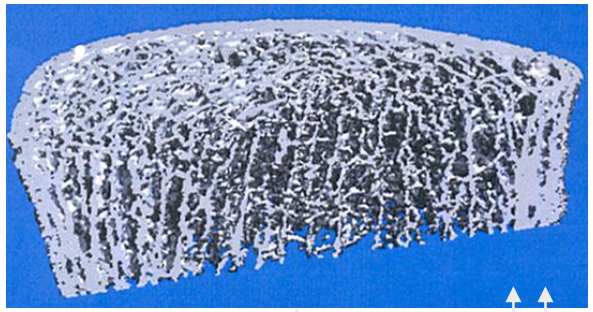
TIBIA CROSS-SECTION

normal bone



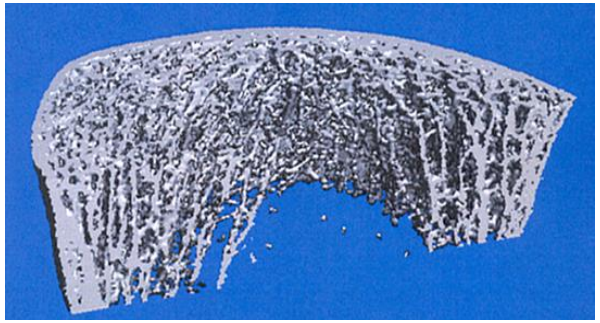
BV/TV	16.1 %
Tb.N.	2.0/mm
Tb.Th.	0.08 mm
Tb.Sp.	0.43 mm

osteopenia



BV/TV	11.3 %
Tb.N.	1.3/mm
Tb.Th.	0.09 mm
Tb.Sp.	0.68 mm

osteoporosis



BV/TV	7.3 %
Tb.N.	0.6/mm
Tb.Th.	0.11 mm
Tb.Sp.	1.47 mm

Courtesy of M.Dambacher - This device is not approved by all health authorities

GUIDELINES FOR THE ASSESSMENT OF BONE DENSITY AND MICROARCHITECTURE IN VIVO USING HRPQCT

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- For using HR-pQCT in clinical studies, a minimum set of parameters should be reported to appropriately characterize the trabecular and cortical bone.
- Appropriate terminology is necessary, - certain parameters have different methods of measurement between scanner generations and thus cannot be directly compared.
- Scan acquisition and analysis, reporting results, quality control and training needs to be standardized

Whittier DE, Boyd SK, Burghardt AJ, et al. Guidelines for the assessment of bone density and microarchitecture in vivo using high-resolution peripheral quantitative computed tomography. Osteoporos Int. 2020;31(9):1607-1627.

THE STRAX HR-PQCT DEVICE

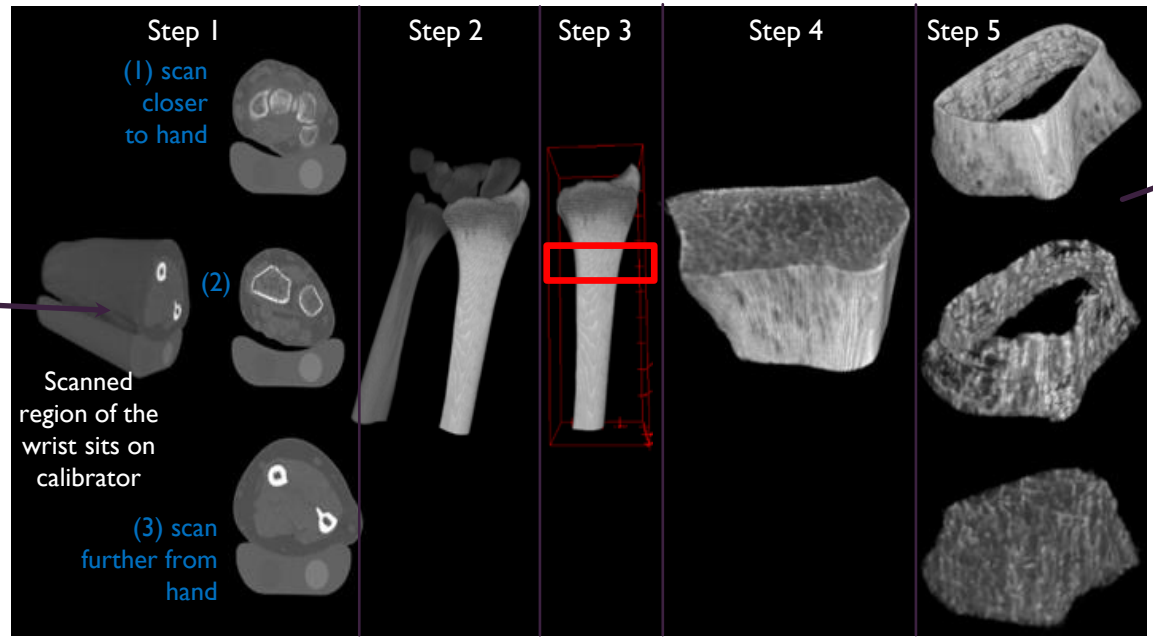
- **High Resolution Images** – 75–80-micron voxel size (FDA, CE, TGA)
- **Negligible Levels of Radiation** – 3-6 microSieverts
- **Fast Scanning - 1 min**
- **Small Footprint** – The device footprint is 23X36 inches
- **Standard 115 V outlet and 'Self Shielded Device' (SSD)-**no additional cooling required
- **Consistent Images** – same quality scanning image globally – no manufacturer-to-manufacturer variations that can impact the performance of HR-pQCT images
- **Bone fragility assessment using an Artificial Intelligence solution and a deep learning framework** – With the new HR-pQCT device, Strax uses proprietary machine learning and deep learning algorithms, to automatically analyze scans with state-of-the-art accuracy and precision
- **Flexibility** – can be used in imaging centers, hospitals, and even a primary care setting –
- **Suitable for patients 50 to 400 lbs**
- **FDA- cleared**

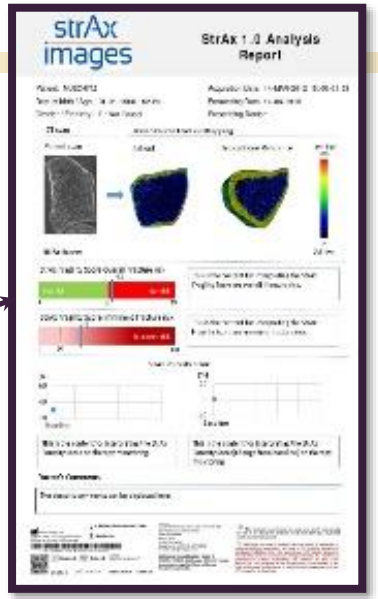
https://us.straxcorp.com/

Introducing Strax Micro CT plus SFS

STRAX FRAGILITY SCORE – PATENT PROTECTED AI ENGINE OVERVIEW

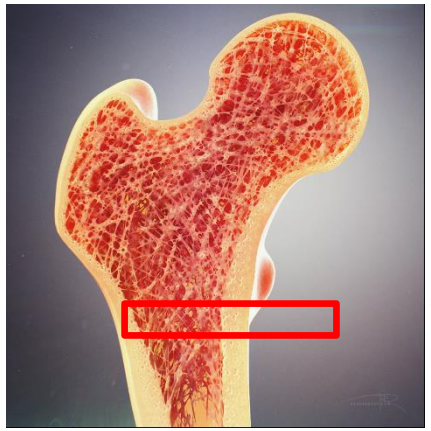
1 minute scan is taken





Step 3 is critical to the value of a bone diagnostic using bone microstructure – Region of Interest (ROI)

A 1% variation in correctly assigning the ROI can change the cortical bone to trabecular bone relationship by 20% (Seeman et al 2017)



Step 3 is separately a blocking patent

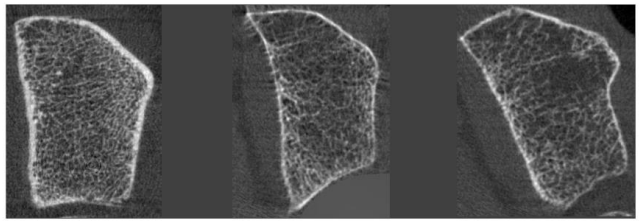
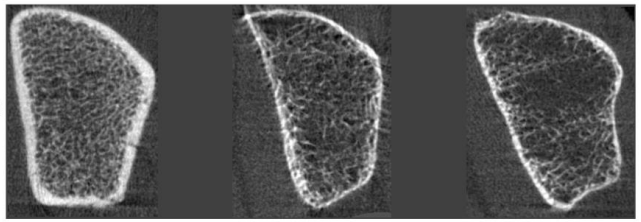
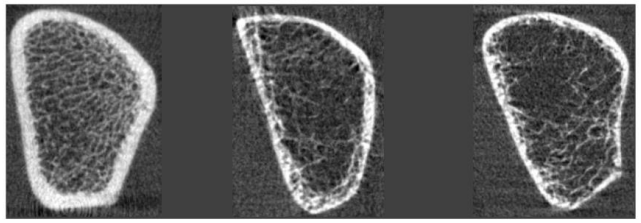
The challenge is to set the ROI correctly for all patients all heights. A set distance back cannot be used, ROI would be different based on height of patient. So, the AI must calculate the length of the patient radius & assign a measure off 10% of the length of the radius back from the hand. Assures same region of interest for all patients, no manual measurement

- **STEP 1** – scan takes 40 single scans wrist. The closer to the hand the bone (radius, ulna, metacarpal) is mainly trabecular (**1**), the further away from the hand it is mainly compact cortex of radius & ulna (**3**)
- **STEP 2 –** all bones 3D reconstructed - all tissue removed
- **STEP 3 –** Radius realigned & critical region of interest assigned
- **STEP 4 –** AI creates 3D region of interest of the radius
- **STEP 5 –** AI separates out compact cortex from transitional zone to trabecular bone for quantitation & Strax Fragility Score (SFS) reported

Patient: Marry Smith
Date of Birth(Age): 1957/06/01(61)
Gender: Female

Scan Date: 2018/11/16
Processing Date: 2018/11/16
Prescribing Doctor: Dr. Ego Seeman

CT Slices

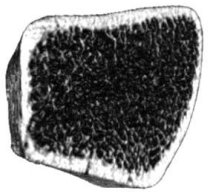
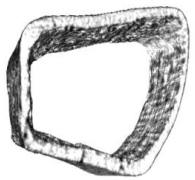
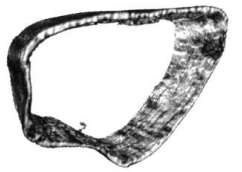
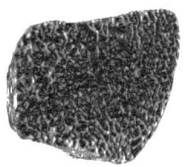
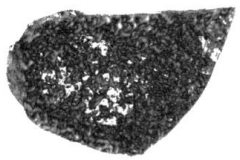
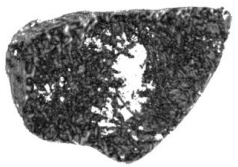
	Healthy Bone Reference	Patient	Decayed Bone Reference
Distal Slice			
Intermediate Slice			
Proximal Slice			

Doctor's Notes:

Patient: Marry Smith
Date of Birth(Age): 1957/06/01(61)
Gender: Female

Scan Date: 2018/11/16
Processing Date: 2018/11/16
Prescribing Doctor: Dr. Ego Seeman

3D Bone Reconstruction

	Healthy Bone Reference	Patient	Decayed Bone Reference
Entire Bone			
Cortical Bone			
Trabecular Bone			

Doctor's Notes:

+ 30 Days Post Analysis Date
StraxCorp Pty Ltd
Suite 5, Level 10, 470 Collins Street
Melbourne, Victoria 3000 Australia
2 Single Use
SN Version 1 REF StrAx1.0 LOT CA00000147
CE665106 16/11/2018 ARTG: 244571 Class IIb
Medical Device & QA Services Ltd
Spring Court, Spring Road
Hale, Cheshire
WA14 2UQ
United Kingdom
Telephone: +44 845 527 5078
E-mail: info@mdqas.com
Software Classification Code A
GMDN: 57812 Radiology DICOM image processing application software
Made in Australia
This analysis report is to be used as a short term single use aid in the diagnosis of bone health disorders by a qualified Health Care Professional.
Although the use of Strax1.0 at the radius is designed to reduce radiation exposure, any use of CT imaging equipment produces radiation, the risks associated with patient exposure to radiation should be assessed and justified by the healthcare professional before subjecting the patient to any such exposure. This analysis is not a diagnosis, it is intended to aid the healthcare professional in their clinical assessment of the CT image for a diagnosis.

QUESTIONS???

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