Update on imaging to assess bone strength

Mary L. Bouxsein, PhD
Center for Advanced Orthopedic Studies
Department of Orthopedic Surgery, Harvard Medical School
MIT-Harvard Health Sciences and Technology Program

@MaryBouxsein
A Crisis in the Treatment of Osteoporosis
S. Khosla and E. Shane, 2016

Addressing the Crisis in the Treatment of Osteoporosis: A Path Forward
S. Khosla et al, 2017

“Despite effective drugs to prevent fracture, many patients...are either not being prescribed osteoporosis medications at all, or when prescribed, refuse to take them...”

“Better identification of high-risk patients”
“Enhance new drug development”
“Reduce burden of fragility fractures”

Hip fracture incidence (US)
All fracture incidence (US)

Leweicki et al, Osteop Int 2018
Leweicki et al, Osteop Int 2020
Review determinants of bone strength

Fracture prediction: beyond BMD

- *Radiofrequency echographic multi-spectrometry (REMS) ultrasound*
- *High-resolution pQCT*
- *Opportunistic CT + Bone strength by CT-FEA (BCT)*
Fractures = structural failure of the skeleton
How do things break?

- Excessive force
- Too many loading cycles
- Fragile (brittle) material
Engineering approach to design a structure

- Consider what loads it must sustain
- Design options
  - Overall geometry
  - Building materials
  - Architectural details
Bones as structures: determinants of whole bone strength

Quantity
size and mass (BMD)

Distribution
shape and geometry
cortical : trabecular mass

Microstructure

Properties of Bone Matrix
matrix mineralization
collagen cross-links
non-collagenous proteins
microdamage
Multiscale hierarchy – integrated for strength
Clinical assessment of bone (strength) today

BMD by DXA

- Bone mass / area (g/cm\(^2\))
- Reflects bone size & matrix mineralization
- Strong predictor of fracture risk in untreated women and men
- Changes in BMD predict anti-fracture efficacy of osteoporosis treatment

- Misses many who fracture
- Doesn’t measure bone macro- or microstructure, distribution of bone density

BMD explains variation in whole bone strength in ex vivo human cadaver studies

Proximal Femur (sideways fall)

Femoral Neck BMD (g/cm²)

Vertebral body (L2)

Spine BMD (g/cm²)

$\text{r}^2 = 0.71$

$\text{r}^2 = 0.79$

Johannesdottir et al 2017; Moro et al, CTI, 1995
Determinants of whole bone strength

- Quantity
  - size and mass (BMD)

- Distribution
  - shape or geometry

  - cortical & trab BMD

- Microstructure

- Properties of Bone Matrix
  - matrix mineralization
  - collagen cross-links
  - non-collagenous proteins
  - microdamage

Non-invasive imaging

- DXA
- CT, CT-FEA
- Ultrasound?

- CT, CT-FEA

- HR-pQCT
Review determinants of bone strength

Fracture prediction: beyond BMD

- *Radiofrequency echographic multi-spectrometry (REMS) ultrasound*
- *High-resolution pQCT*
- *Opportunistic CT + Bone strength by CT-FEA (BCT)*
Radiofrequency echographic multi-spectrometry (REMS)

Estimated BMD, T-scores (fem neck, lumbar spine)

FDA approval in 2018 for BMD, T-score & monitoring (Echolight)

Diez-Perez et al, Aging Clin Exp Res, 2019
Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck

M. Di Paolo1,2; D. Gatti3; G. Viapiana1; L. Cianferotti1; L. Cavalli1; C. Caffarel1; F. Conversano1; E. Quarta4; P. Piscani2; G. Girasole1; A. Guidi1; M. Manfredini1; G. Avioli1; M. Mutacci-Cerinic2; G. Bianchi2; R. Nuni1; S. Gonnelli3; M. L. Brandi1; M. Muratore3; M. Rossini3

Original Contribution

A NOVEL ULTRASOUND METHODOLOGY FOR ESTIMATING SPINE MINERAL DENSITY

FRANCESCO CONVERSANO, ROBERTO FRANCHINI, ANTONIO GRECO, GIULIA SOLOPERTO, FERNANDA CIRIACI, ERNESTO CASCARRO, MATTEO AVENATTI, MARIA DANIELA RINNA, PAOLA PISANI, MARCO DI PAOLA, ANTONELLA GIMALDI, LAURA QUARTA, EUGENIO QUARTA, MAURIZIO MURATORE, PASCALE LACOFFRE, AND SERGIO CASCARRO

*National Research Council, Institute of Clinical Physiology, Lecce, Italy; **Echolight srl, Lecce, Italy; ***O.U. of Rheumatology, “Galeno” Hospital, San Cesareo di Lecce, ASL LE, Lecce, Italy; and **Laboratoire d’Imagerie Biomédicale, Sorbonne Universités, UPMC 06, INSERM, CNRS, Paris, France

Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context

Bernard Cortet1, Elaine Dennisson1,2, Adolfo Diaz-Perez3,4, Méda Lacquet5,6, Maurizio Muratore7,8, Xavier Nogue2,9, Diana Ovejero Crespo10, Eugenio Quarta11, Maria Luisa Brandi12,13

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-019-01294-4

Radiofrequency echographic multi-spectrometry for the in-vivo assessment of bone strength: state of the art—outcomes of an expert consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)

Adolfo Diaz-Perez; Maria Luisa Brandi; Nasser Al-Daghri; Jaime C. Branco; Olivier Bruyère; Loredana Cavalli; Cyrus Cooper; Bernard Cortet; Bess Dawson-Hughes; Hans Peter Dimai; Stefano Gonnelli; Peyman Hadji; Philippe Halbout; Jean-Marc Kaufman; Andreas Kurth; Medea Lacquet; Stefania Maggini; Radmila Matijevic; Jean-Yves Reginster; René Rizzoli; Thomas Thierry
REMS vs DXA for diagnosis of osteoporosis
(n= 4307, age 30-90, multicenter study in Europe)

Cortet et al, Bone, 2020

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fem neck</td>
<td>85.5%</td>
<td>94.5%</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>89%</td>
<td>94.3%</td>
</tr>
</tbody>
</table>

Diagnostic sensitivity: with and without osteoporosis (DXA gold standard)

Concordance: normal, osteopenia, osteoporosis (DXA gold standard)

<table>
<thead>
<tr>
<th></th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fem neck</td>
<td>82.7%</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>83.4%</td>
</tr>
</tbody>
</table>
REMS vs DXA for prediction of fracture risk

N=1516 (age 30-90)

192 Fx over 3.7 yr follow-up

Outcomes
• Hip and spine DXA
• Hip and spine REMS

Examined fracture (n=175) and no-fracture groups (n=350)

Adami et al, Bone, 2020
# REMS vs DXA for prediction of fracture risk

<table>
<thead>
<tr>
<th></th>
<th>Fx (n=175)</th>
<th>No Fx (n=350)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.2</td>
<td>67.3</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>25.0</td>
<td>24.6</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Spine DXA T-score</td>
<td>-2.8</td>
<td>-2.2</td>
<td>&lt;0.0001</td>
<td>1.7 (1.2-2.5)</td>
</tr>
<tr>
<td>Spine REMS T-score</td>
<td>-2.9</td>
<td>-2.2</td>
<td>&lt;0.0001</td>
<td>2.6 (1.8-3.8)</td>
</tr>
<tr>
<td>FN DXA T-score</td>
<td>-2.2</td>
<td>-2.0</td>
<td>0.03</td>
<td>2.7 (1.7-4.2)</td>
</tr>
<tr>
<td>Fem REMS T-score</td>
<td>-2.3</td>
<td>-1.9</td>
<td>0.02</td>
<td>2.8 (1.8-4.4)</td>
</tr>
</tbody>
</table>

Adami et al, Bone, 2020
Outline

Review determinants of bone strength

Fracture prediction: beyond BMD

• *Radiofrequency echographic multi-spectrometry (REMS) ultrasound*
• *High-resolution pQCT*
• *Opportunistic CT + Bone strength by CT-FEA (BCT)*
“Virtual bone biopsy”
61-82 µm voxel size
~ 100 to 140 µm resolution
2-3 min scan; < 5 µSv
HR-pQCT discriminates osteopenic women with and without history of fragility fracture
(age = 69 yrs, n=35 with prev frx, n=78 without fracture)

* p < 0.05 vs fracture free controls

Boutroy et al, JCEM (2005)
Osteopenic by DXA BMD

70 yr old woman from OFELY cohort, image courtesy of S. Boutroy
HR-pQCT Measures of Bone Microarchitecture Predict Fracture: Systematic Review and Meta-Analysis

Nicholas Mikolajewicz,1,2 Nick Bishop,3 Andrew J Burghardt,4 Lars Folkestad,5 © Anthony Hall,6 Kenneth M Kozloff,7 © Pauline T Lukey,8 Michael Molloy-Bland,9 Suzanne N Morin,10 © Amaka C Offiah,3 Jay Shapiro,11 Bert van Rietbergen,12 Kim Wager,13 Bettina M Willie,1,14 © Svetlana V Komarova,1,2 © and Francis H Glorieux1 ©

- 40 studies
- ~ 13,000 individuals (1291 – 3253 with fracture)
- Age 11 – 85 yrs

- Fracture associated deficits in total and trabecular vBMD, tibial cortical parameters, µFEA failure load
- Improved reproducibility needed for routine longitudinal monitoring

“Our study supports the use of HR-pQCT in clinical fracture prediction”
Bone Microarchitecture International Consortium (BOMIC)

- Prospective population-based cohorts with HR-pQCT imaging, DXA-BMD and fracture incidence
- Women and men
- Canada, Sweden, France (3 cohorts), Switzerland, US
Bone micro-architecture and strength predict incident fracture

- International consortium of 7 cohorts with HR-pQCT and incident fracture
- 7254 subjects (64% W)
- Age: 68 ± 9 yrs
- Follow up: 4.5 ± 2.6 yr
- Fem Neck aBMD by DXA
- HR-pQCT of non-dominant ultradistal radius and tibia
- 756 incident fractures
  - 14% in osteoporotic (t-score ≤ -2.5)
  - 60% in osteopenic (-2.5 < t-score < -1)
  - 26% in normal (t-score ≥ -1)

Samelson et al, Lancet Diab Endo, 2019
Bone micro-architecture and strength predict incident fracture independent of fem neck BMD

Independent of femoral neck BMD, fracture risk increased 20-45% per SD decrease in bone microarchitecture

Hazard Ratio for Fracture (per SD) (adjusted for age, sex, ht, wt + fnBMD)

Samelson et al, Lancet Diab & Endocrin, 2019
N = 6802 (69 ± 10 yrs, 71% W)

609 incident fragility fx over ~5 yrs

HR-pQCT density + structure
Bone strength by µFEA
FN aBMD
FRAX

µFRAC
• HR-pQCT density + structure + µFEA
• FN aBMD
• Sex, age, ht, wt, prior fx

µFRAC’
• HR-pQCT density + structure
• FN aBMD
• Sex, age, ht, wt, prior fx

µFRAC’’
• HR-pQCT density + structure
• Sex, age, ht, wt, prior fx

Whittier et al (under review, JBMR)
HR-pQCT & fragility “phenotypes”

Clusters

Dissimilarity

“Healthy Bone”

Cortical fragility
HR 3.19 (2.0, 4.9)

Trabecular fragility
HR 2.0 (1.4, 2.9)

‘Osteoporotic’ Trabecular
‘Healthy’ Bone
‘Osteoporotic’ Cortical

Cumulative Hazard of Fracture

Time since scan (years)

Whittier et al, ASBMR 2020
Race/ethnicity-related differences in microarchitecture

White woman

Black woman

Putman, et al, JBMR 2013; Popp et al, Bone 2017; 2019
Pathophysiology of fragility in Type 2 diabetes?

Burghardt et al, JCEM (2010); Patsch et al, JBMR (2013); Yu et al, Osteop Int (2015); Shanbhogue et al, Eur J Endo (2016); Samelson, Bouxsein et al, JBMR (2017); Samakkarnthai et al, JCEM 2020
Outline

Review determinants of bone strength

Fracture prediction: beyond BMD

- *Radiofrequency echographic multi-spectrometry (REMS) ultrasound*
- *High-resolution pQCT*
- *Opportunistic CT + Bone strength by CT-FEA (BCT)*
Finite Element Analysis (FEA)

Bone strength by QCT-FEA
Biomechanical Computed Tomography (BCT)

Images from Fidler et al, Radiology, 2015
Experimentally measured femoral strength vs FEA-predicted strength
(sideways fall, 73 human femora, aged 55 to 98 yrs)

$\text{r}^2 = 0.78$
$p < 0.001$
$\text{SEE} = 900 \text{ N}$

Johannesdottir et al, Bone 2017
### BCT vs femoral BMD: hip fracture prediction

<table>
<thead>
<tr>
<th>STUDY GROUP</th>
<th>FEM NECK BMD HAZARD RATIO (95% CI)</th>
<th>BCT FEM STRENGTH HAZARD RATIO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older men (Mr OS)¹ 40 hip fx vs 210 controls</td>
<td>4.4 (2.4-9.1)</td>
<td>6.5 (2.3-18.3)</td>
</tr>
<tr>
<td>Older men (AGES cohort)²</td>
<td>3.7 (2.5-5.6)</td>
<td>3.5 (2.3-5.3)</td>
</tr>
<tr>
<td>Older women (AGES cohort)²</td>
<td>2.7 (1.9-3.9)</td>
<td>4.2 (2.6-6.9)</td>
</tr>
</tbody>
</table>

* Adjusted for age, race

1Orwoll et al, JBMR 2009; 2Kopperdahl et al, JBMR 2014
## BCT vs spine BMD: vertebral fx prediction

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Spine BMD Hazard Ratio (95% CI)</th>
<th>BCT vert strength Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older men (Mr OS)(^1)</td>
<td>3.3 (2.1- 5.2)</td>
<td>7.3 (3.7-14.5)</td>
</tr>
<tr>
<td>63 VFx vs 243 controls (DXA-BMD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older men + women (FHS)(^2)</td>
<td>1.8 (1.0 – 3.3)</td>
<td>3.8 (1.5 – 9.2)</td>
</tr>
<tr>
<td>26 VFx vs 62 controls (CT-aBMD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older men (AGES)(^3)</td>
<td>1.7 (1.2 – 2.5)</td>
<td>2.2 (1.5 – 3.2)</td>
</tr>
<tr>
<td>Older women (AGES)</td>
<td>2.3 (1.7 – 3.2)</td>
<td>2.8 (1.8 – 4.3)</td>
</tr>
<tr>
<td>171 hip fx vs 877 control (Ct-Tb.BMD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, race

---

\(^1\)Orwoll et al, JBMR 2009; \(^2\)Allaire et al, Osteop Int 2019; \(^3\)Kopperdahl et al, JBMR 2014
Can routine CT procedures can be used for bone strength evaluation?

Each Year in Medicare:
- 12 million hip/spine CT scans
- 1.5 million DXA diagnostic tests

Each Year in US:
7.8 million patients with previous hip/spine CT meet NOF screening guidelines

CMS (2018) Part B National Summary Data File, Code Range: 03) Radiology (70000 - 79999); scaled from all Medicare Part-B to all Medicare Age 65+ only. Hip CT = any abdomen/pelvic CT, with or without contrast; Spine CT = any thoracic, lumbar, or chest CT, without contrast. For DXA, 40% of reported DXA in Medicare is for diagnostic screening, 60% for monitoring (Zhang *JBMR* 27:858–64, 2012). NOF = National Osteoporosis Foundation
Routine CT scans for osteoporosis diagnosis: fem neck

**CT Enterography**

- T-score from CT Scan
- \( R^2 = 0.84 \)
- Women (n=71)
- Men (n=65)

**CT Colonoscopy**

- T-score from CT Scan
- \( R^2 = 0.84 \)
- n=136

Weber et al, Am J Gastroenterology, 2014

Fidler et al, Radiology, 2015
FOCUS cohort
(Fracture, Osteoporosis and CT Utilization Study)

• Evaluate technical feasibility and diagnostic performance of biomechanical CT (BCT) in large managed care setting

• Hip Fx Cases and Controls with CT scan and DXA within 3 yrs
  – 80 different CT scanners!

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Fracture</td>
<td>Fracture</td>
<td>No fracture</td>
<td>Fracture</td>
</tr>
<tr>
<td>N</td>
<td>1019</td>
<td>903</td>
<td>458</td>
<td>403</td>
</tr>
<tr>
<td>Age (years) mean</td>
<td>74.0</td>
<td>79.5</td>
<td>75.7</td>
<td>80.3</td>
</tr>
<tr>
<td>BMI (kp/m²), mean</td>
<td>27.9</td>
<td>25.0</td>
<td>27.7</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Adams et al, JBMR 2018
Prediction of hip fracture risk similar for DXA-BMD and BCT

<table>
<thead>
<tr>
<th>Classification</th>
<th>Women Hazard Ratio</th>
<th>Men Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCT Hip BMD T-score</td>
<td>2.4 (2.0-2.9)</td>
<td>2.7 (2.0-3.8)</td>
</tr>
<tr>
<td>Femoral Strength</td>
<td>3.6 (2.8-4.6)</td>
<td>3.0 (2.2-4.3)</td>
</tr>
<tr>
<td>Femoral Strength (adj for BMD)</td>
<td>2.4 (1.5-4.0)</td>
<td>3.3 (1.8-5.9)</td>
</tr>
<tr>
<td>DXA Hip BMD T-score</td>
<td>2.3 (1.9-2.9)</td>
<td>2.4 (1.9-3.1)</td>
</tr>
</tbody>
</table>

Compared to CT-based hip BMD alone, adding femoral strength identified ~20% more patients who suffered a hip fracture.

Adams et al, JBMR 2018
How has BCT been used to date?

Osteoporosis screening in clinical setting
- CT Colonography
- IBD patients (CT Enterography)
- Prostate cancer patients (PET-CT)
- Liver transplant (Triple phase CT)
- Pre-op CT for spinal Fusion


Fracture prediction
Nine studies showing significant association of low bone strength with hip and/or vertebral fracture; equivalent to DXA-BMD

What is status of BCT today?

- FDA approval for diagnosis of osteoporosis, monitoring & prediction of fracture risk
- CMS approval (reimbursed by Medicare)
- Established CPT codes
- O.N. Diagnostics recognized as a Medicare-enrolled Independent Diagnostic Testing Facility (IDTF)

FDA-approved outcomes from BCT analysis
- Hip and spine bone strength, *with established thresholds for normal, low and fragile bone strength*
- DXA-equivalent FN and TH aBMD; T-scores; Z-scores
- Spine trabecular vBMD
- Fracture risk assessment (not increased, increased, high)
Where is all the health care data coming from?

Big Data in Health Care
Generates Exabytes of Data

- Genomic Sequencing
- Medical Imaging
- Health Records
- Payor Records
- Medical Devices
- Smartphones
- Wearables
- Search Engine Data
- Pharmaceutical Research

2,314 Exabytes in 2020
153 Exabytes in 2013

Source: "Harnessing the Power of Data in Health."

machine learning
artificial intelligence
deep learning
Opportunistic Use of CT Imaging for Osteoporosis Screening and Bone Density Assessment

A Qualitative Systematic Review

Elizabeth B. Gausden, MD, Benedict U. Nwachukwu, MD, MBA, Joseph J. Schreiber, MD, Dean G. Lorich, MD, and Joseph M. Lane, MD

CURRENT CONCEPTS REVIEW

Clinical Use of Opportunistic Computed Tomography Screening for Osteoporosis

Paul A. Anderson, MD, David W. Polly, MD, Neil C. Binkley, MD, and Perry J. Pickhardt, MD

Investigation performed at the University of Wisconsin, Madison, Wisconsin

Value-Added Opportunistic CT: Insights Into Osteoporosis and Sarcopenia

Robert D. Boutin¹, Leon Lenchik²

OBJECTIVE. The purpose of this article is to review the emerging field of opportunistic CT, which can be used to screen patients for osteoporosis and sarcopenia.

CONCLUSION. Although body composition measurements are not routinely obtained using CT, quantitative assessment of bone and muscle biomarkers on CT can add value to patient care. Automated bone and muscle measurements promise to transform the everyday practice of radiology without resulting in additional cost or radiation exposure for patients.
Simultaneous Screening for Osteoporosis at CT Colonography: Bone Mineral Density Assessment Using MDCT Attenuation Techniques Compared With the DXA Reference Standard

Perry J Pickhardt,1 Lawrence J Lee,1 Alejandro Muñoz del Río,1 Travis Lauder,1 Richard J Bruce,1 Ron M Summers,2 B Dustin Pooler,1 and Neil Binkley1

1University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
2Radiology and Imaging Sciences Department, National Institutes of Health Clinical Center, Bethesda, MD, USA

Opportunistic Osteoporosis Screening at Routine Abdominal and Thoracic CT: Normative L1 Trabecular Attenuation Values in More than 20,000 Adults

Samuel Jang, MD • Peter M. Graffy, BA, MPH • Timothy J. Ziemlewicz, MD • Scott J. Lee, MD • Ronald M. Summers, MD, PhD • Perry J. Pickhardt, MD

Automated opportunistic osteoporotic fracture risk assessment using computed tomography scans to aid in FRAX underutilization

Noa Dagan1,2,3,4, Eldad Elnekave2,4,5,6, Noam Barda1,2,3, Orna Bregman-Amitai5, Amir Bar5, Mila Orlovsky5, Eitan Bachmat2 and Ran D. Balicer1,3
Automated abdominal CT imaging biomarkers for fx prediction

\[ N = 9,223 \ (57 \pm 8 \text{ yrs, 56\% W}) \]
  - Non-contrast CT, 120 kvp, GE

686 MOP over 8.8 yrs
  - 219 hip fx

CT Outcomes
- L1 trabecular bone attenuation
- L1 VAT/SAT (V/S) ratio
- L3 muscle attenuation

Electronic health record review
- Fracture outcomes
- FRAX (\pm BMD)

Pickhardt et al, Radiology, 2020
L1 BONE
HR 2.1 (1.8, 2.4)

L3 MUSCLE
HR 1.9 (1.6, 2.2)

FRAX
HR 2.5 (2.1, 2.9)

Pickhardt et al, Radiology, 2020
Automated opportunistic osteoporotic fracture risk assessment using computed tomography scans to aid in FRAX underutilization

Noa Dagan, Eldad Elnekave, Noam Bar, Orna Bregman-Amitai, Amir Bar, Mila Orlovsky, Eitan Bachmat and Ran D. Balicer

N = 48,227 (69 ± 10 yrs, 52% W)

5,106 MOP and 1,901 hip fx over ~5 yrs

CT Outcomes
- Vertebral fracture (96.5%)
- Simulated DXA T-score (84.3%)
- Min L1-L4 trabecular vBMD (62.3%)
- VCF + simulated DXA (83.6%)

CT Meta Data: Age + Sex

Electronic health record review
- FRAXnb (no BMD)
Automated opportunistic osteoporotic fracture risk assessment using computed tomography scans to aid in FRAX underutilization

Noa Dagan, Eldad Elnekave, Noam Barada, Orna Bregman-Amitai, Amir Bar, Mila Orlovsky, Eitan Bachmat and Ran D. Balicer

N = 48,227 (69 ± 10 yrs, 52% W)

5,106 MOP and 1,901 hip fx over ~5 yrs

CT Outcomes
- Vertebral fracture (96.5%)
- Simulated DXA T-score (84.3%)
- Min L1-L4 trabecular vBMD (62.3%)
- VCF + simulated DXA (83.6%)

CT Meta Data: Age + Sex

Electronic health record review
- FRAXnb (no BMD)

Table 2 | Discriminatory performance (%) of the FRAXnb, CT-based and FRAXnb-CT prediction tools

<table>
<thead>
<tr>
<th>Discriminatory measuresa</th>
<th>FRAXnb prediction tool</th>
<th>CT-based prediction tool</th>
<th>FRAXnb-CT prediction tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major osteoporotic fracture outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (95% CI)</td>
<td>69.1 (68.0-70.2)</td>
<td>70.9 (69.9-72.0)</td>
<td>72.3 (71.3-73.3)</td>
</tr>
<tr>
<td>Absolute risk cutoff</td>
<td>4.9</td>
<td>10.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Sensitivity (95% CI)b</td>
<td>64.1 (62.4-65.9)</td>
<td>66.5 (64.7-68.2)</td>
<td>67.4 (65.7-69.1)</td>
</tr>
<tr>
<td>Specificity (95% CI)b</td>
<td>64.4 (64.2-64.7)</td>
<td>64.7 (64.5-64.9)</td>
<td>64.8 (64.6-65.1)</td>
</tr>
<tr>
<td>PPV (95% CI)b</td>
<td>17.7 (17.0-18.5)</td>
<td>18.4 (17.6-19.2)</td>
<td>18.6 (17.8-19.5)</td>
</tr>
<tr>
<td>NPV (95% CI)b</td>
<td>93.7</td>
<td>94.2</td>
<td>94.3</td>
</tr>
</tbody>
</table>

Fully automated CT scan analysis showed similar AUC, sensitivity, specificity, PPV and NPV to FRAXnb

Analysis is based on the test dataset, which consisted of n=24,113 individuals. The CIs were calculated using the bootstraps as detailed in the Methods. All measures were evaluated and averaged across the ten imputed datasets of the test dataset. For a proportion at high risk, which was set by applying the National Osteoporosis Foundation cutoffs to the FRAXnb-CT prediction tool.
Challenges with opportunistic CT ± AI/ML

- Defining ‘intervention’ thresholds
- Skeletal site variation
- Manual vs fully automated analyses
- Scan calibration
  - none, asynchronous, synchronous
- Validation in diverse cohorts
- Clinical pathway?
Whole Bone Strength

Bone Mass
BMD, BMC

Morphology
Geometry
Microarchitecture

Tissue Level Mechanical Properties

Mineralization

Microdamage

Organic matrix

DXA

QCT

BCT

REMS

HR-pQCT
Conclusions

**REMS**
- Innovative point-of-care device, equiv to BMD
- Needs validation in diverse cohorts
- Operator training & standardization?

**HR-pQCT imaging**
- Predicts fx, but limited by availability of devices….rationale for innovation?
- Pathophysiology

**BCT**
- Ready to go
- Could expand # of patients evaluated and treated for skeletal fragility

**Innovations in opportunistic CT imaging +/- AI/ML show promise & potential**
- Standardization & validation needed
- Detection of VFx

“Better identification of high-risk patients” …improve treatment rates…reduce fracture burden
Harvard Medical School
Fjola Johannesdottir, Brett Allaire, Dennis Anderson, Katelyn Burkhart, Douglas Kiel, Elizabeth Samelson, Elaine Yu, Kristin Popp

USARIEM
Julie Hughes, Katie Taylor, Katelyn Guerriere

ON Diagnostics
Tony Keaveny, David Lee, David Kopperdahl

FNIH-ASBMR SABRE Project
Dennis Black, Richard Eastell, Douglas Bauer, Eric Vittenhoff, Lucy Lu, Lilly Liu, Gayle Lester

Funding from NIH-NIAMS and the Department of Defense
BCT Clinical Workflow — Two Pathways

**Hospital or Imaging-Center Providers**
Provider subcontracts with OND for the BCT service

a) Physician orders the BCT test from Provider / Radiology

b) Provider sends CT to OND

c) OND performs the technical analysis and returns results to Provider

d) Provider interprets BCT results and sends medical report to ordering Physician

**OND’s National Lab Service**
(Medicare-enrolled Independent Diagnostic Testing Facility)
No contracts

a) Physician orders the BCT test from OND

b) OND retrieves CT from imaging facility

c) OND performs the technical analysis and returns BCT results or medical report* to ordering Physician

* Results are available nationwide. Interpreted Medical Report available only in California; elsewhere, physician should arrange for medical interpretation.
Automatic identification of VFx and BMD

$R^2 = 0.83$

Sollman et al, JBMR 2022
Imaging and femoral strength

- 20 studies
  - 14 stance, 13 fall loading
- Sample size: 7 to 76
- Age range: 21 – 100 yrs

<table>
<thead>
<tr>
<th>Method</th>
<th>Stance loading $r^2$</th>
<th>Sideways fall loading $r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA (aBMD)</td>
<td>0.51 – 0.66</td>
<td>0.61 – 0.94</td>
</tr>
<tr>
<td>CT (vBMD, BMC)</td>
<td>0.45 – 0.82</td>
<td>0.30 – 0.87</td>
</tr>
<tr>
<td>CT-FEA (Failure Load)</td>
<td>0.54 – 0.94</td>
<td>0.77 – 0.90</td>
</tr>
</tbody>
</table>

“3D CT-FEA consistently provides slightly better prediction of femoral strength than densitometric or other structural variables”

Bouxsein et al, Osteop Int 2019