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Bone Quality by QCT and HR-pQCT: Translation to Multicenter Clinical Research

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Introduction

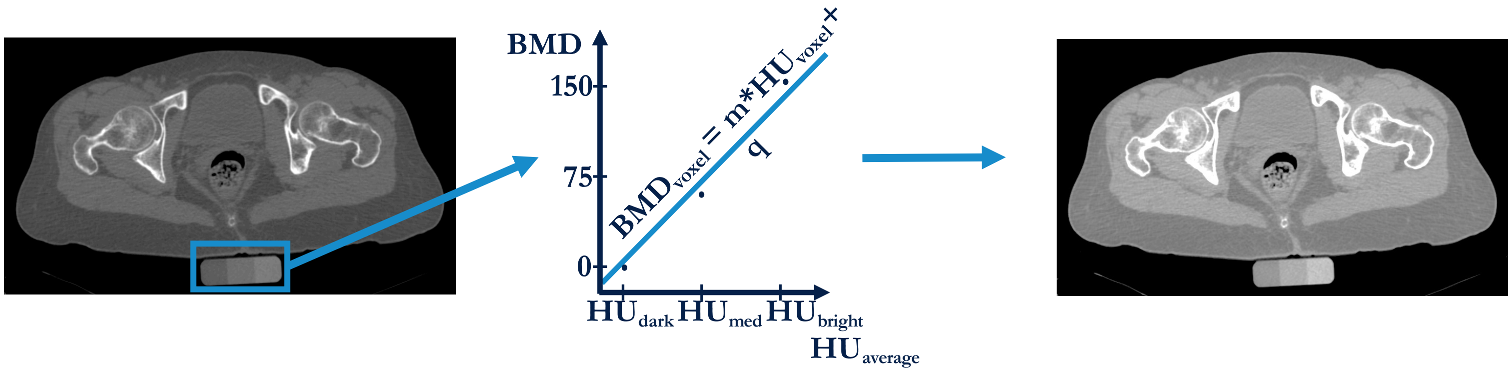
- QCT and HR-pQCT are X-ray based imaging techniques used to asses bone quality at a macro-scale (mm) and micro-scale (µm)
- From images, we calculate bone structure, density and strength
- Bone measurements used to evaluate bone quality, investigate age-, sex, and race-related differences, monitor drug therapies, and assess fracture risk
- Currently, QCT and HR-pQCT lack of some degrees of standardization, which prevents them to be used clinically
  - Cross-scanner calibration (QCT)
  - Acquisition procedures (HR-pQCT)

Bone Quality by $\boxed{\text{QCT}}$ and HR-pQCT: Translation to Multicenter Clinical Research

Scanner Cross-Calibration

Quantitative Computed Tomography (QCT)

- Pad phantom positioned under the patient allows transformation from Hounsfield Units to bone mineral density (mg/cm^{3}HA)



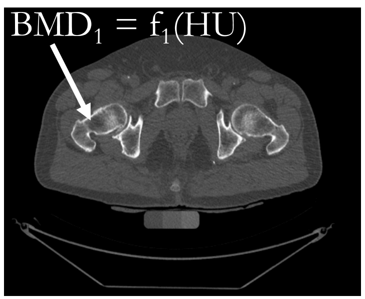
- Volumetric quantification of bone mineral density and geometry separately for cortical and trabecular bone
- Assessment of bone strength through finite element models (geometry and mechanical properties directly derived from images)

Adams 2009; Lang 2010

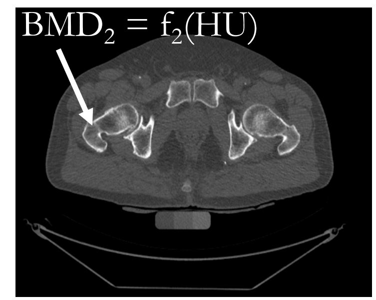
Why Do We Need Cross-Scanner Calibration?

GE VCT 64 detectors

Siemens PET-CT 16 detectors



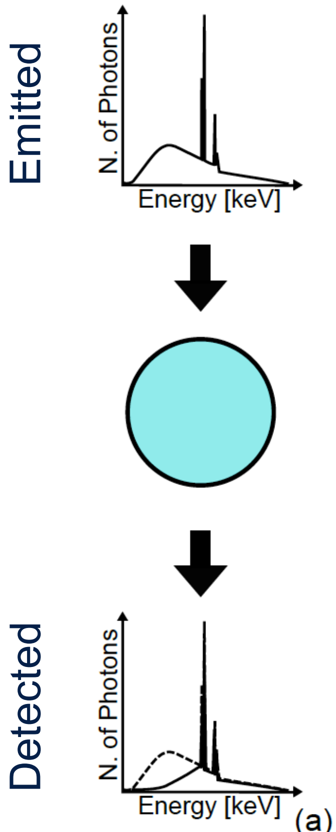
$$\boxed{BMD_{GE} \neq BMD_{Siemens}}$$



- Inter-scanner acquisitions
  - Multicenter studies, longitudinal studies with scanner substitution
- Inter-scanner differences are systematic (hardware and software) and patient-specific (beam hardening effect)

Beam Hardening Effect and Patient's Size

- Attenuation of X-rays depends on energy of emitted photons, body tissue and size, and location of the region of interest

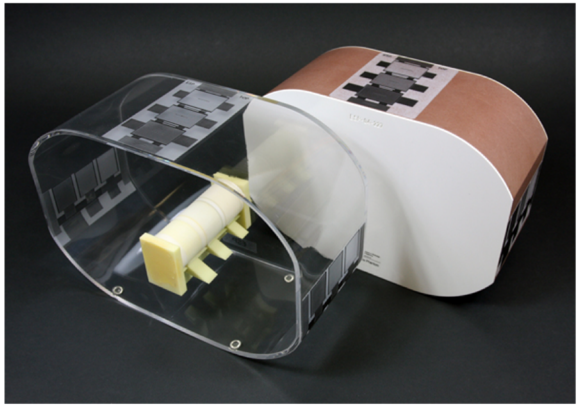


Hsieh 2009; Levi 1982

Aim of Cross-Calibration

- To create **correction equations** that allows us to reduce *inter*-scanner errors to *intra*-scanner precision errors

- Different anthropomorphic phantoms are used to cross-calibrate
- Equations are calculated regressing bone mineral density from images acquired on different scanners
- Inter-scanner differences remain and body size has an effect



QRM European Spine Phantom

- There is no current standard solution for QCT scanner cross-calibration

Birnbaum 2014, Carpenter 2014

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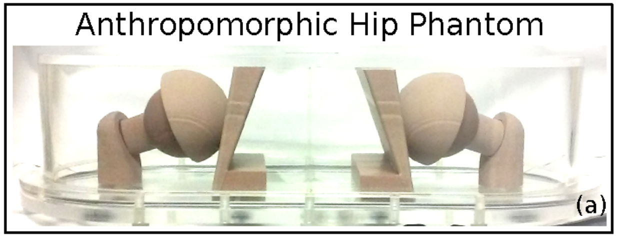
Anthropomorphic Hip Phantom (AHP)



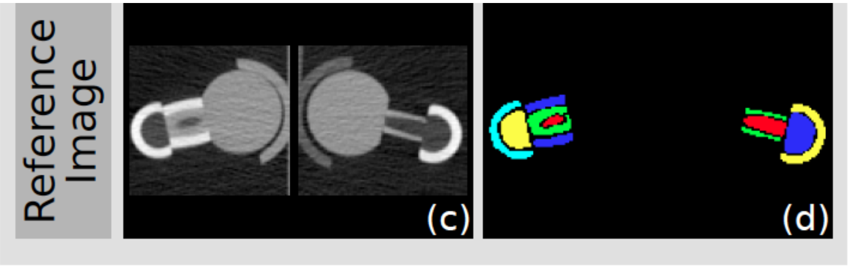
- Simulates the anatomy and the beam-hardening environment of the pelvis
- Calibration hip to calculate cross-calibration regression
- Test hip inserts to assess the quality of the regression for old and young subjects
- Three body circumferences simulating normal, medium-sized and obese subjects

Experiment

- Anthropomorphic hip phantom scanned on 4 scanners
  - GE VCT 64 System and Siemens Biograph/Definition Flash at UCSF and Mayo Clinic
- Different configuration of age (old/young) and size (no/small/large)
- Cross-calibration procedure
  - Calculated regression line on BMD of phantom *calibration* hip
  - Tested regression line on BMD of phantom *test* hip
  - Applied regression line to BMD of 16 women (age: 64±3 yrs) scanned on GE and Siemens scanners at UCSF

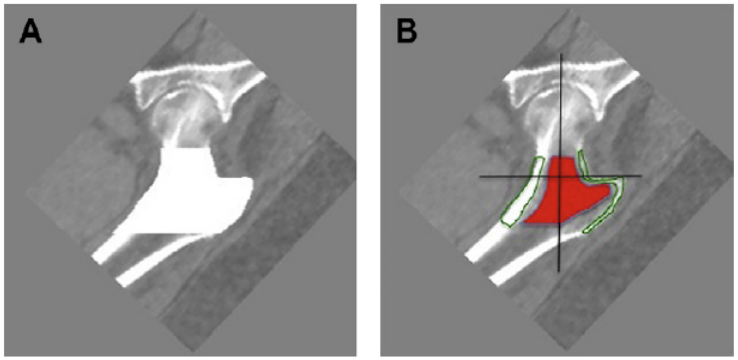
Calculating BMD For Phantom Images

- Same region segmented in all images using affine registration
- One reference image semi-automatically segmented avoiding partial volume effect voxels



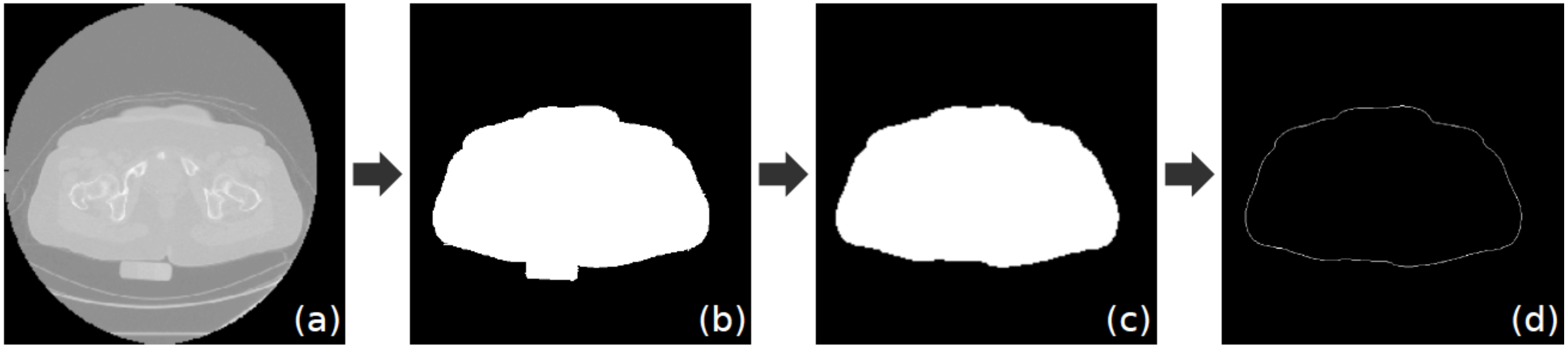
Calculating BMD and Body Size For Subjects

- Calculation of BMD (threshold-driven region growing)



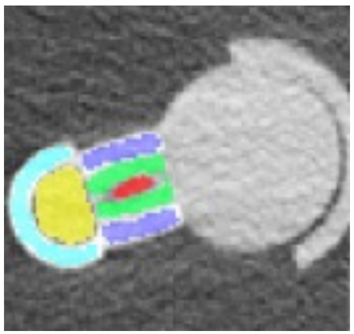
Lang 2010, Carpenter 2014

- Calculation of body size (morphologic operators and Hough transform)

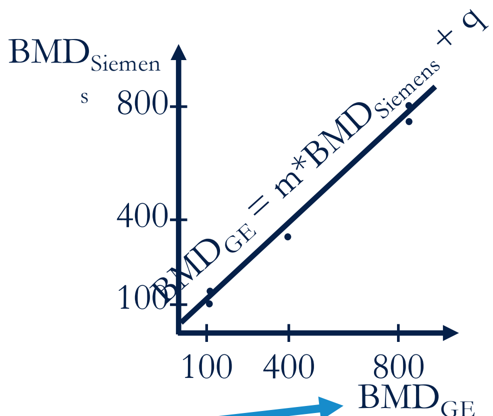


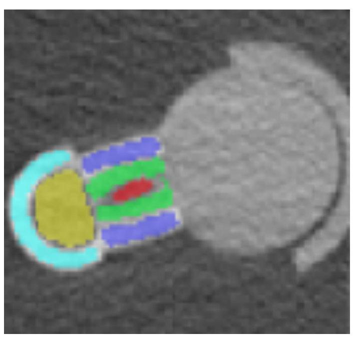
Calculating Inter-Scanner Corrections

- Regression lines for BMD of images from different scanners



Calibration Hip - Siemens





Calibration Hip - GE

Regression line applied to
- test hip
- human subjects

Results – Calibration Hip BMD and Inter-Scanner Corrections

- The most stable scanner with respect to body size was the Siemens at UCSF → reference scanner
- For the other scanners, *intra*-scanner differences of BMD were larger for large body size

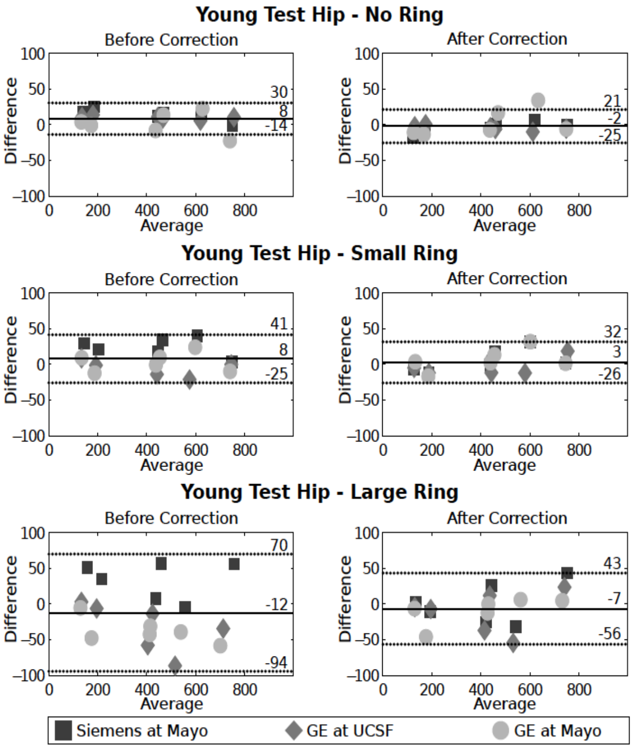
- *Inter*-scanner differences of BMD were larger
  - For phantom with large girdle
  - For cortical bone

- In *inter-scanner regressions*, slopes and intercepts were larger for large ring and GE system
- For subjects, we used inter-scanner regression calculated from phantom with old test hip and no girdle

$$BMD_{GEcrosscal} = 0.998 \times BMD_{GE} - 17.126$$

Results – Testing Corrections on Test Hip and Subjects

- Before correction, inter-scanner differences were significant in all compartments, both for old and young test hip
- After correction, differences reduced considerably, although not significantly



- Mean differences between BMDs decreased after correction, but standard deviation remained the same

	Ct. BMD [mg/cm³]	Tb. BMD [mg/cm³]
Before Correction	17.95±17.50	14.42±5.96
After Correction	-5.81±14.35	-3.76±6.67

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Discussion

- Novel anthropomorphic hip phantom simulates anatomy and beam hardening effect of the pelvis to calculate cross-scanner corrections
- *Intra*- and *inter*-scanner BMD measurement differences increase when body size increases and are larger for cortical bone
- Cross-scanner correction removed systematic inter-scanner differences, but patient specific differences are still present

Next Steps

- Linear regression does not reduce patient-specific errors in cross-scanner calibration → different approach to the problem

- Currently testing combined cross calibration on 120 patients scanned at UCSF and Mayo Clinic on 4 different scanners

Publications

- Bonaretti S., Carpenter D.R., Saeed I., Burghardt A.J., Yu L., Bruesewitz M., Khosla S., Lang T. **Novel Anthropomorphic Hip Phantom Corrects Systemic Interscanner Differences in Proximal Femoral vBMD.** Phys Med Biol. 59(24), 7819-34. 2014.
- Carpenter R.D., Saeed I., Bonaretti S., Schreck C., Keyak J.H., Streeper T., Harris T.B., Lang T.F**. Inter-scanner Differences in In Vivo QCT Measurements of the Density and Strength of the Proximal Femur Remain After Correction with Anthropomorphic Standardization Phantoms.** Med Eng and Phys. 36(10), 1225-32. 2014.

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Bone Quality by QCT and $\boxed{\text{HR-pQCT:}}$ Translation to Multicenter Clinical Research

Standardization of Acquisition – Operator Precision in Reference Line Positioning

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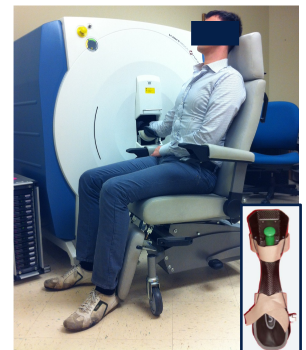
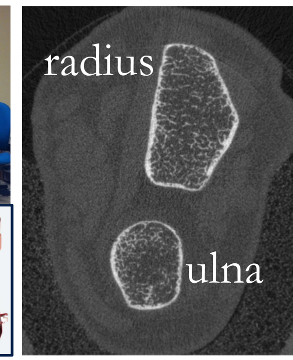
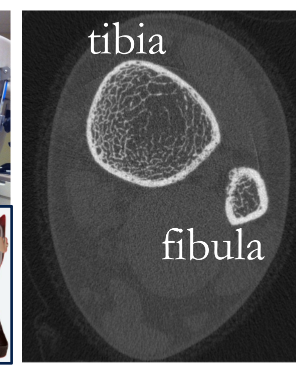
High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)

- High resolution (82μm) *in-vivo* acquisition of distal radius and tibia with low radiation dose (3μSv)

- Morphometric measurements
  - Ct.Th., Ct.Ar., Ct.Po., Tb.N., Tb.Th., Tb.Sp.
- Bone density measurements
  - Tt.BMD, Ct.BMD, Tb.BMD
- Biomechanical measurements
  - $L_{failure}$, $Ct.LF_{prox}$, $Ct.LF_{dist}$

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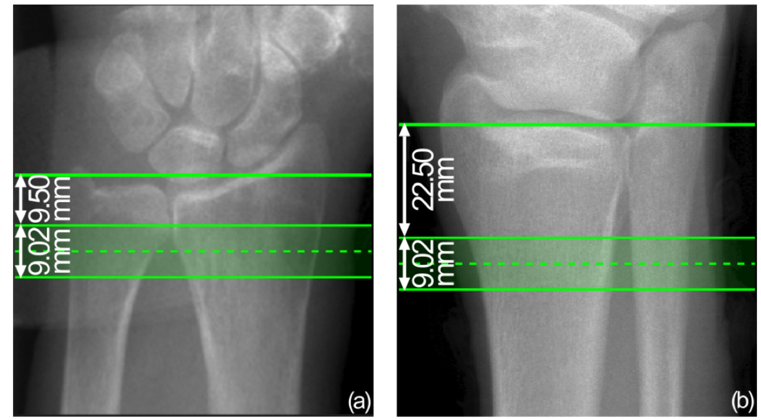
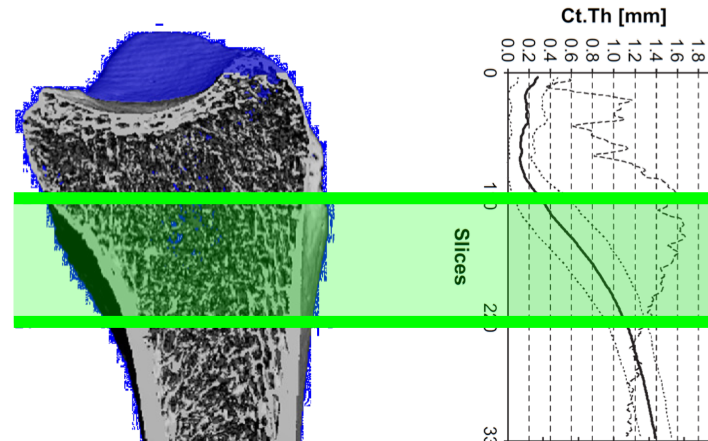
Operator Determines Region to Be Scanned

- Operator positions a reference line at a defined landmark on scout view image
- Scanned region is at a fixed distance from reference line



- Morphometric and densitometric measurements change considerably along bone axis
- Effects on data comparability in cross-sectional studies, in particular multicenter studies
- → ***Precise*** positioning of reference line



Modified from Boyd, 2008

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Previous Literature and Aim

- Scan/rescan total precision errors are smaller
  - For tibia (<5.2%) than for radius (<6.3%)
  - For densitometric (<1.5%) than for structural (<4.5%) measurements
- No study has systematically evaluated the role of HR-pQCT operators in reference line positioning

- To analyze the role of operator ***precision*** in a multicenter HR-pQCT setting
  - Variability of reference line positioning
  - Consequent effects on bone measurements

Boutroy 2005, Khosla 2006, MacNeil 2008, Engelke 2012, Burghardt 2013

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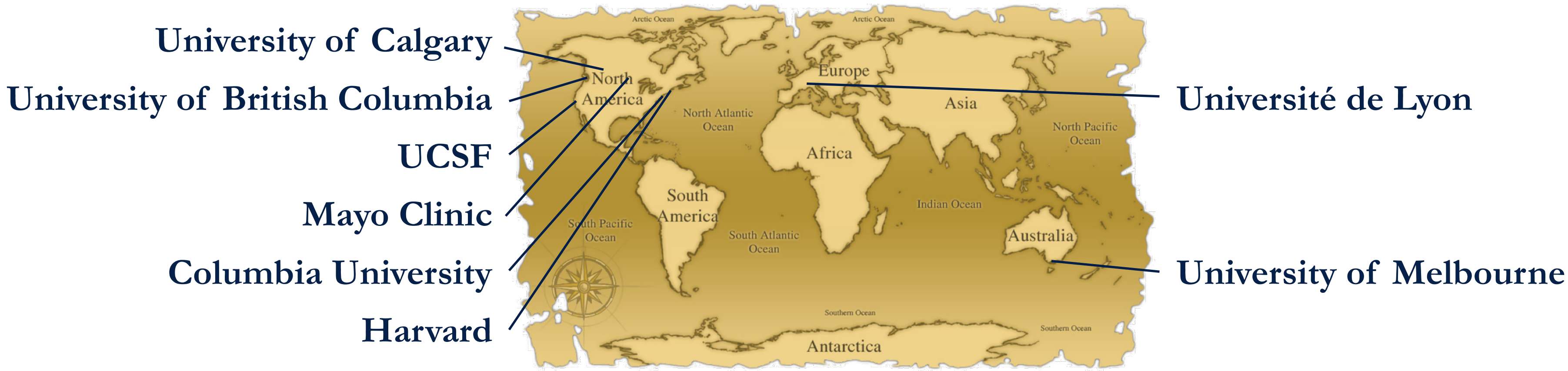
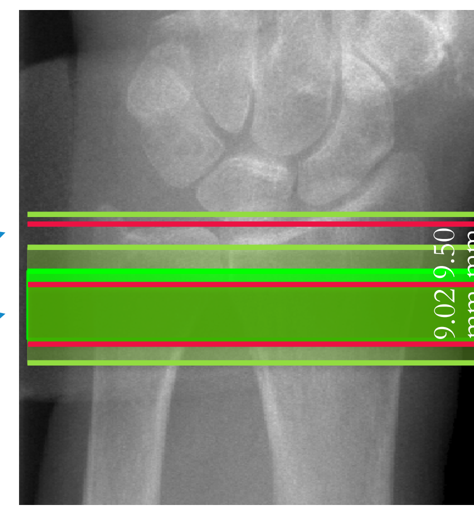
Operators and Imaging

- Operators from eight imaging centers

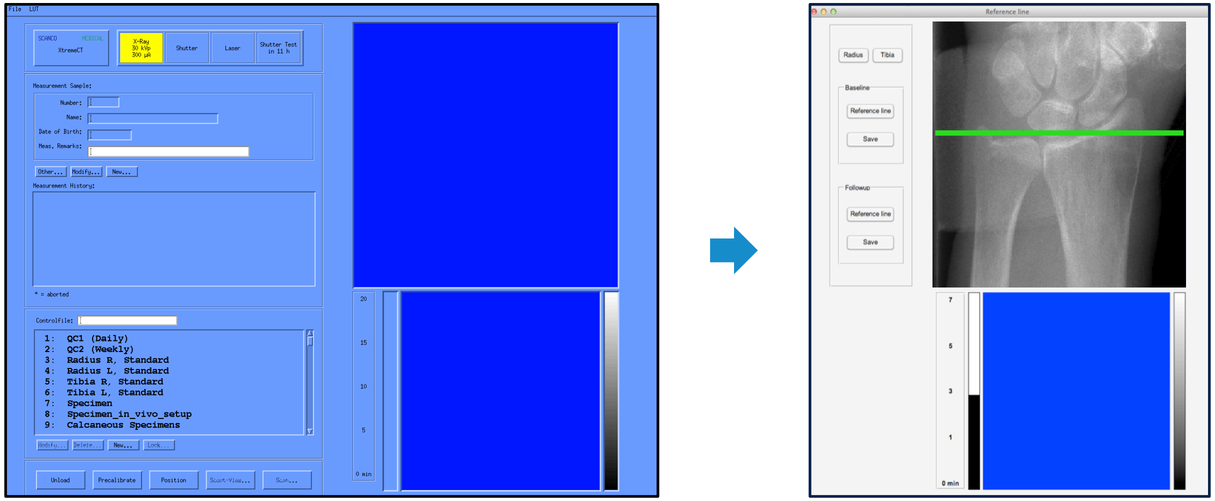


- Image acquisition
  - 2 operators at UCSF and Mayo Clinic
  - 56 male and female subjects (71±4 yrs)
  - Double-length stacks (220 slices)
- Simulation outcome measures
  - Reference line positioning
  - Effect on bone parameters



Simulation and Experiment

- Software reproducing acquisition software GUI



- Short-term intra-operator precision
  - Same scout images randomly repeated 3 times
  - 45 images for radius and 48 images for tibia
- Inter-operator precision
  - 50 images for radius and 55 images for tibia

Results - Positioning Precision

POSITIONING PRECISION ERROR	Intra-operator $SD_{RMS}[mm]$	Inter-operator $SD_{RMS}[mm]$
Radius	0.24	0.68
Tibia	0.13	0.30

- Positioning precision error for radius was double then for tibia
- Inter-operator positioning precision was double than inter-operator positioning precision

Results – Bone Parameter Measurements

BONE PARAMETERS ERRORS	Intra-operator CV_{RMS}[%]	Inter-operator CV_{RMS}[%]	Scan-rescan CV_{RMS}[%]
Radius			
Tt.BMD	1.39	3.69	0.89
Ct.Th	3.17	8.40	2.10
$Ct.FL_{dist}$	2.65	6.37	4.31
Tibia			
Tt.BMD	0.26	0.61	0.43
Ct.Th	0.94	1.97	1.25
$Ct.FL_{dist}$	0.92	2.02	4.01

- Precision errors for bone parameters followed the trend of positioning precision errors (radius>tibia, inter-op>intra-op)
- Ct.Th had the highest variation for the radius
- Errors due to reference line positioning are equivalent too, or exceed, the in-vivo precision error (scan/rescan)

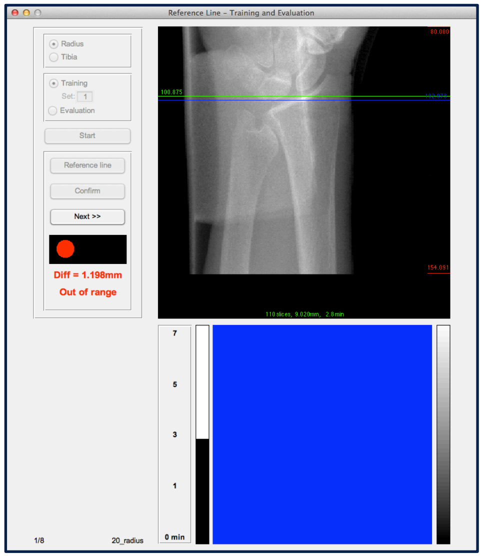
Discussion and Second Step

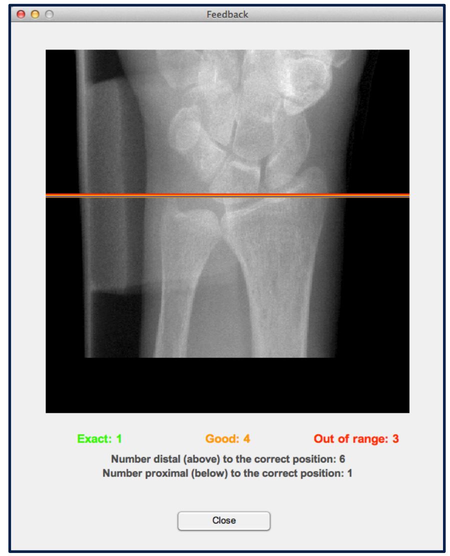
- Operator variability in reference line positioning is a major component of in-vivo precision error, for both radius and tibia
- Inter-operator variability is significantly greater than intra-operator variability, for both radius and tibia

- How can we reduce inter-operator variability?

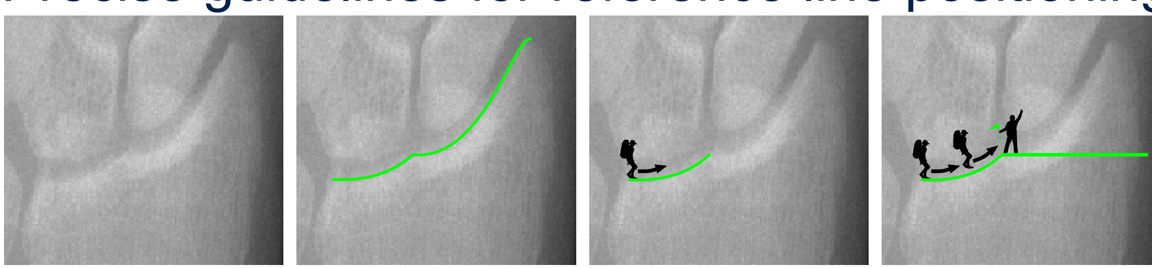
Reference Line – Training and Evaluation

- Standard platform for operator training and certification





- Precise guidelines for reference line positioning



Operators and Experiments

- Six operators involved in the MrOS study with no previous experience with HR-pQCT
- MrOS operators trained on Reference Line – Training and Evaluation and obtained certification

- After certification, operators took part in the same experiments as the experienced operators (intra- and inter-reproducibility)

Results - Positioning Precision

POSITIONING PRECISION ERROR	Intra-operator SD_{RMS}[mm]	Inter-operator SD_{RMS}[mm]
Radius	0.24/0.28	0.68/0.30
Tibia	0.13/0.11	0.30/0.16

Experienced operators/New operators

- Intra-operator errors for new operators were similar errors of experienced operators
- Inter-operator positioning errors for new operators approached intra-operator precision errors

Results – Bone Parameter Measurements

BONE PARAMETERS ERRORS	Intra-operator CV_{RMS}[%]	Inter-operator CV_{RMS}[%]	Scan-rescan CV_{RMS}[%]
Radius			
Tt.BMD	1.39/1.50	3.69/2.09	0.89
Ct.Th	3.17/3.46	8.40/4.90	2.10
$Ct.FL_{dist}$	2.65/3.03	6.37/3.37	4.31
Tibia			
Tt.BMD	0.26/0.31	0.61/0.30	0.43
Ct.Th	0.94/0.52	1.97/1.02	1.25
$Ct.FL_{dist}$	0.92/0.75	2.02/1.32	4.01

Experienced operators/New operators

- Precision errors for bone parameters followed the trend of positioning precision errors (radius>tibia, inter-op~intra-op)

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Discussion and Third Step

- Inter-operator positioning precision errors were half for operators who used our training software to learn standard positioning procedures
- Our training platform could be a useful tool to homogenize operator positioning, especially for multicenter studies

- How can we make the tool available for the HR-pQCT community?

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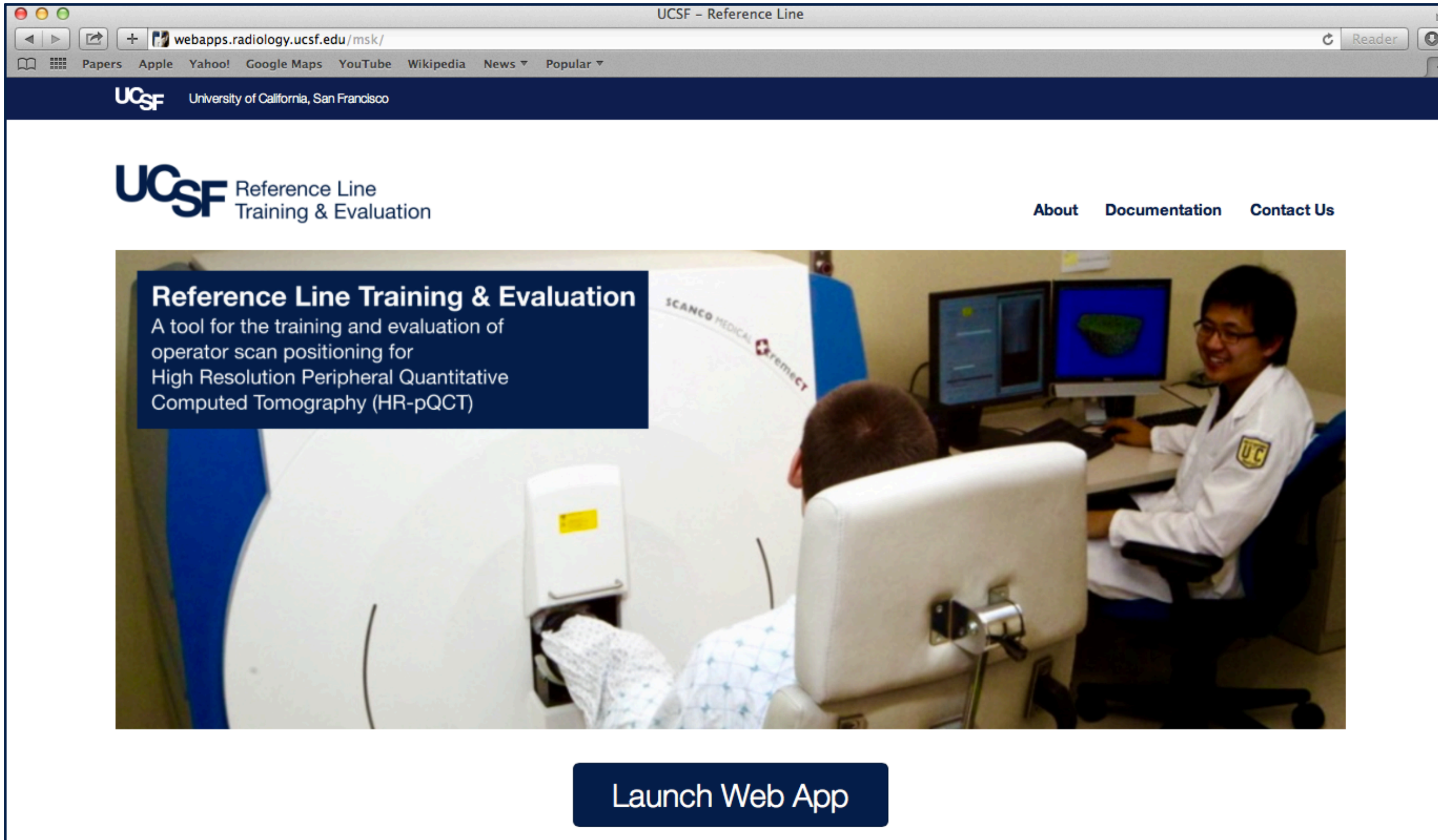
Reference Line – Training and Evaluation Web Application

webapps.radiology.ucsf.edu/refline



Next Steps and Related Works

- Add modules to webapp for hand and knee (OA), and pediatric subjects
- Change radius anatomical landmarks to decrease precision errors

- Anatomically standardized positioning of the region to be scanned (%limb length)
- Detection and correction of patient motion in images, especially radius
- Development of pediatric protocol
- Scanner cross-calibration

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Publications

- Bonaretti S., Vilayphiou N., Chan C. M., Yu A., Nishiyama K., Liu D., Boutroy S., Ghasem-Zadeh A., Boyd S.K., Chapurlat R., McKay H., Shane E., Bouxsein M.L., Black D.M., Majumdar S., Orwoll E.S., Lang T.F., Khosla S., Burghardt A.J. **Operator Variability in Scan Positioning Is a Major Component of HR-pQCT Precision Error and Is Reduced by Standardized Training.** Under review in Osteoporosis International.
- Bonaretti S., Holets M., Majumdar S., Lang T.F., Khosla S., Burghardt A.J. **Comparability of HR-pQCT Bone Quality Measures Improved by Scanning Anatomically Standardized Regions.** Ready for submission.

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