

Individualized assessment of osteoporotic fracture risk at the spine using ultra-low-dose MDCT imaging techniques and non-dedicated routine MDCT exams

FINAL REPORT

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1 General Information

PI Project numbers:

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Project title:

Individualized assessment of osteoporotic fracture risk at the spine using ultra-low-dose MDCT imaging techniques and non-dedicated routine MDCT exams

Names of the applicants:

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2 Summary

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing an individual to an increased risk for fracture. Osteoporotic fractures, particularly at the spine and hip, are associated with a reduced quality of life and an increased morbidity and mortality. Thus, osteoporosis is classified as a public health problem in our ageing society [1].

Dual Energy X-ray Absorptiometry (DXA)-based Bone Mineral Density (BMD) measurements and corresponding T-scores are limited in their prediction of fracture risk as BMD/T-score of subjects with versus without osteoporotic fractures overlap [2]. Vertebral BMD assessment and Finite Element Modelling (FEM) in Multi-Detector Computed Tomography (MDCT) exams performed at least as well as DXA-based T-score to predict incident vertebral fractures [3, 4].

The purpose of our research project was twofold:

Firstly, we developed iterative image reconstruction techniques and advanced CT acquisition models (e.g. virtual sparse sampling CT and dual-layer spectral CT) which allowed BMD, bone texture analysis, and FEM in ultra-low dose images to predict vertebral-specific fracture risk. Our study results suggested that a 50% radiation dose reduction through reduced tube current and a 90% radiation dose reduction through sparse sampling can be used to adequately predict FEM-based vertebral bone strength as compared to a standard clinical routine MDCT protocol [5]. Furthermore, our findings indicated that the sparse sampling-based method performs better than the tube current-reduction method in generating images required for FEM-based bone strength prediction models and clinical assessment of reading spinal pathologies [6-8].

We also demonstrated that spectral-detector based x-ray absorptiometry (SDXA) can differentiate patients with versus without osteoporotic fractures [9]. Thus, SDXA could be a useful tool for opportunistic osteoporosis screening. Furthermore, we investigated the diagnostic accuracy of iodine-corrected vertebral BMD measurements derived from non-dedicated contrast-enhanced phantomless dual-layer spectral CT (DLCT) examinations [10]. Converted BMD derived from contrast-enhanced DLCT examinations and adjusted for individual vessel iodine concentrations showed a high agreement with non-enhanced DLCT-BMD, suggesting that opportunistic BMD measurements are feasible in non-dedicated contrast-enhanced DLCT examinations.

Secondly, we developed a fully automated pipeline to use non-dedicated clinical routine MDCT exams for opportunistic osteoporosis screening. A fully automated framework (<https://anduin.bonescreen.de>) has been developed for MDCT images of the spine by the research group. The framework includes fully automated labelling and segmentation of vertebrae using a convolutional neural network, extraction of trabecular and integral volumetric bone mineral density (vBMD), and MDCT-based areal BMD (aBMD) using asynchronous calibration. BMD measurements using this automated framework showed good agreement with standard QCT-

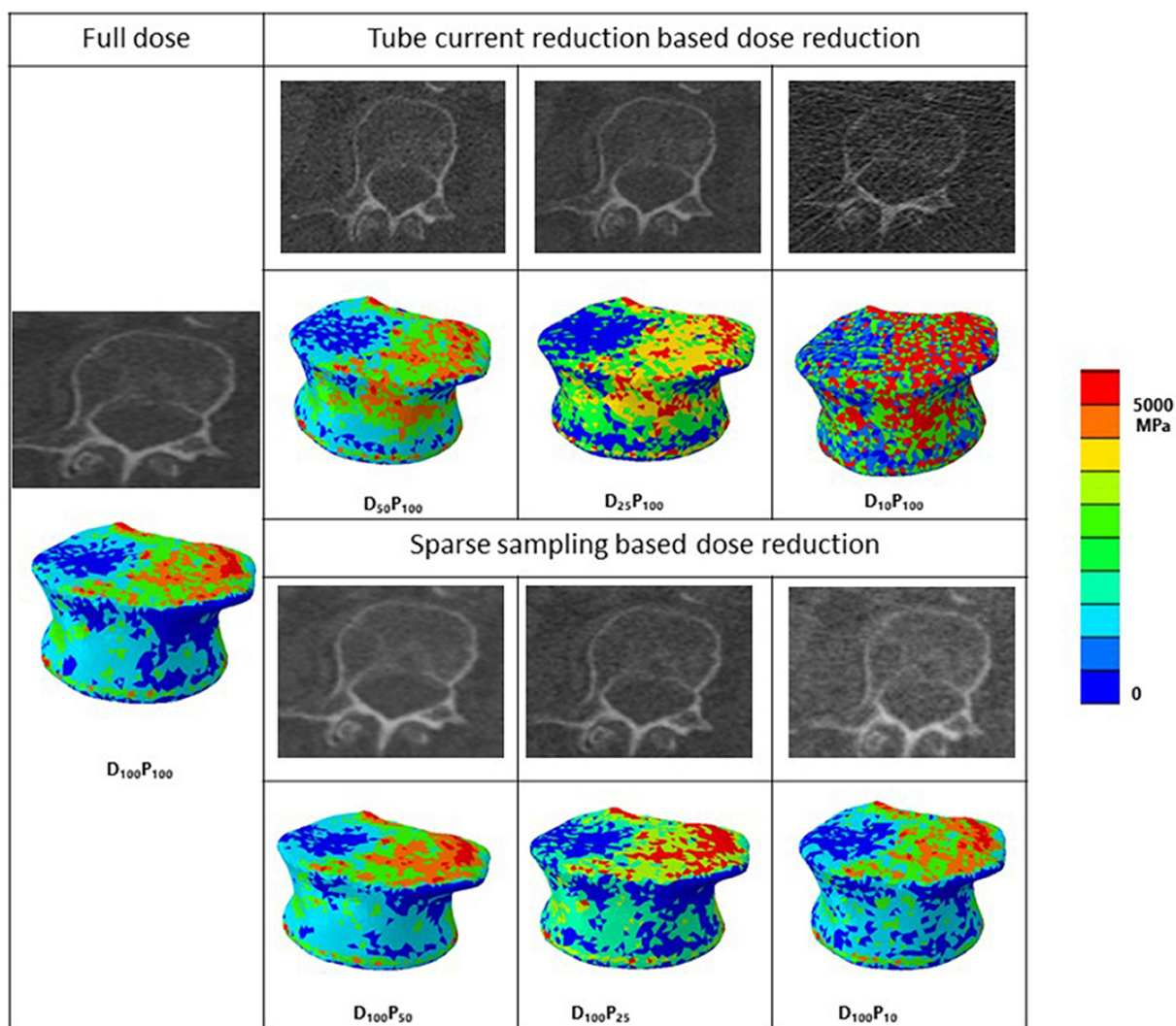
based BMD measurements [11]. Furthermore, opportunistic assessment of vBMD, trabecular bone texture features, and FEM-based vertebral failure load using the framework yields substantial reproducibility [12-14]. All measures performed significantly better as predictors for vertebral fractures compared to DXA [15]. We established vBMD threshold values at different spinal levels, derived from clinical routine MDCT for the prediction of incident vertebral fractures [16]. No significant difference between vertebral levels was observed and was highest at the thoracolumbar junction. Lastly, we investigated the performance of BMD measurements based on our automated framework in vertebral osteoporotic fracture prediction as compared to fracture prevalence-based prediction models. Vertebral fracture prediction based on automatically extracted vBMD outperformed prediction models based on vertebral fracture status and count [17].

Our studies underline the feasibility and importance of ultra-low dose CT imaging for bone strength prediction in the context of osteoporosis and our developed convolutional neural network framework allows reproducible opportunistic osteoporosis screening in clinical routine MDCT data.

3 Progress Report

Work package 1: Ultra-low dose MDCT simulations

We investigated the impact of dose reduction in MDCT images by using virtual tube current reduction or sparse sampling on vertebral bone strength prediction using FEM [5]. Routine MDCT data covering the lumbar spine were used for virtual sparse sampling and virtually reduced tube current. MDCT images were computed using statistical iterative reconstruction (SIR) with reduced dose levels at 50, 25, and 10% of the tube current and original projections, respectively. Results from this study suggested that a 50% radiation dose reduction through reduced tube current and a 90% radiation dose reduction through sparse sampling can be used to still adequately predict vertebral bone strength. Our findings indicate that the sparse sampling-based method performs better than the tube current-reduction method in generating images required for FEM-based bone strength prediction models.



MDCT images along with corresponding representative 3-D contour plots of Young's modulus distribution along the axial direction after material mapping at different dose levels in the vertebra. Red color region shows the maximum, whereas blue color region shows the minimum Young's modulus values in the bone. D, tube current reduction-based dose reduction; P, Sparse sampling-based dose reduction [5].

Similar results were observed at the proximal femur as clinically important osteoporotic fracture site [18]. Our simulations indicate that up to 50% reduction in radiation dose through sparse sampling can be used for FEM-based prediction of femoral failure load.

The same method was applied in side projects:

1. MDCT images with 50% of original tube current or projections still allowed for accurate diagnosis of degenerative changes at the spine [7]. Sparse sampling may be more promising for further radiation dose reductions, since no degenerative changes were missed with 10% of initial projections.
2. The use of sparse sampling for low-dose MDCT in patients with spinal instrumentation facilitated considerable reductions in radiation exposure [8]. The use of 25% of the initial

projections resulted in no missed complications related to spinal instrumentation and allowed high diagnostic confidence.

3. MDCT scans can be used for assessing the composition of the paravertebral musculature in the clinical context of cachexia and sarcopenia. Sparse sampling down to 5% of the initial projections may still be used for muscle composition measurements [6].

Work package 1: Dual-layer spectral CT for osteoporosis screening

In a pilot study, we investigated whether a dual-layer spectral CT scout scan-based areal BMD estimation method, called Spectral-detector based x-ray absorptiometry (SDXA), can differentiate patients with versus without osteoporotic fractures [9]. Patients with osteoporosis were evaluated by assessing the areal BMD at the spine (L1 to L4) in patients presenting at least one fracture and comparing these results to the areal BMD of age- and gender-matched controls. The average areal BMD of patients presenting fractures, measured with the scout scan-based method ($0.86 \pm 0.17 \text{ g cm}^{-2}$), was found to be significantly lower than the average BMD of the control group ($1.00 \pm 0.17 \text{ g cm}^{-2}$, $p = 0.043$). Thus, the SDXA method for DXA-equivalent areal BMD estimation allows to distinguish patients presenting osteoporotic fractures. Considering the total number of CT examinations worldwide, SDXA could be a useful tool for opportunistic osteoporosis screening.

Furthermore, we investigated the diagnostic accuracy of iodine-corrected vertebral BMD measurements derived from non-dedicated contrast-enhanced phantomless dual-layer spectral CT (DLCT) examinations [10]. Vertebral volumetric DLCT-BMD was measured in native, arterial, and portal-venous scans of 132 patients (63 ± 16 years; 32% women) using virtual monoenergetic images (50 and 200 keV). For comparison, conventional BMD was determined using an asynchronous QCT calibration.

BMD values derived from contrast-enhanced phases using conversion equations adjusted for individual vessel iodine concentrations showed a high agreement with those from non-enhanced scans in Bland-Altman plots. Mean absolute errors of DLCT-BMD were 3.57 mg/ml for the arterial ($R^2 = 0.989$) and 3.69 mg/ml for the portal-venous phase ($R^2 = 0.987$) (conventional BMD: 4.70 [$R^2 = 0.983$] and 5.15 mg/ml [$R^2 = 0.981$]). Thus, converted BMD derived from contrast-enhanced DLCT examinations and adjusted for individual vessel iodine concentrations showed a high agreement with non-enhanced DLCT-BMD, suggesting that opportunistic BMD measurements are feasible even in non-dedicated contrast-enhanced DLCT examinations.

Work Package 2: Opportunistic osteoporosis screening in clinical MDCT routine data

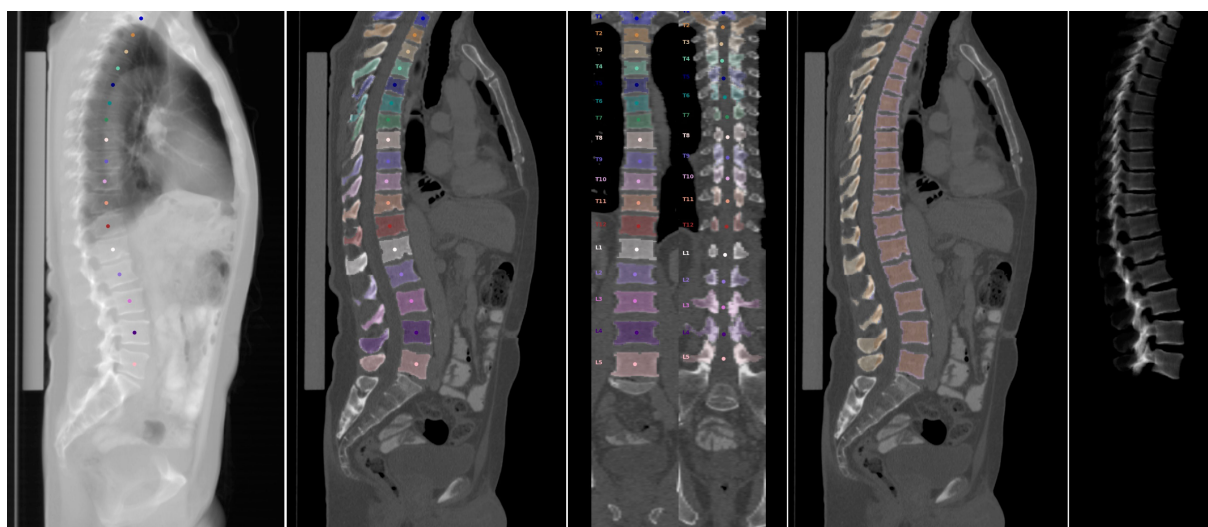
A fully automated framework (<https://andu.in.bonescreen.de>) has been developed for MDCT images of the spine by the research group (with additional funding from the ERC-StG-2014 “iBack”, PI: Jan Kirschke). The framework includes fully automated labelling and segmentation of vertebrae using a convolutional neural network, extraction of trabecular and integral volumetric bone mineral density (vBMD), and MDCT-based areal BMD (aBMD) using asynchronous calibration.

First, the accuracy of the artificial neural network for fully automated detection of the presence and phase of iodinated contrast agent in routine abdominal MDCT scans was evaluated [19]. Application of contrast agent resulted in significant BMD biases (all $p < .001$; portal-venous (PV): RMSE 18.7 mg/ml, mean difference 17.5 mg/ml; arterial (AR): RMSE 6.92 mg/ml, mean difference 5.68 mg/ml). After the fully automated correction, this bias was no longer significant ($p > .05$; PV: RMSE 9.45 mg/ml, mean difference 1.28 mg/ml; AR: RMSE 3.98 mg/ml, mean difference 0.94 mg/ml).

Second, BMD measurements using this automated convolutional neural network algorithm were compared with those derived from dedicated QCT, and non-calibrated Hounsfield Units (HU) measurements from vertebral bodies in routine MDCT data [11]. The intraclass correlation coefficient (ICC) for QCT-based BMD versus automated BMD indicated better agreement (ICC = 0.913) than the ICC for QCT-based BMD versus non-calibrated HU (ICC = 0.704). Bland-Altman analysis showed data points from 95.1% of the included patients within the limits of agreement of -23.2 to 25.0 mg/cm³ for QCT-based BMD versus automated BMD. Thus, automated opportunistic osteoporosis screening in routine MDCT of various scanner setups is feasible.

Third, we investigated the reproducibility of texture features and BMD extracted from trabecular bone in the thoracolumbar spine in routine clinical MDCT in a single scanner environment [12]. Patients who underwent two routine clinical thoraco-abdominal MDCT exams at a single scanner with a time interval of 6 to 26 months ($n=203$, 131 males; time interval mean, 13 months; median, 12 months) were included in this observational study. The developed framework was used for automated spine labeling and segmentation (T5-L5), asynchronous Hounsfield unit (HU)-to-BMD calibration, and correction for the intravenous contrast medium phase. Vertebral volumetric BMD and six texture features [variance_{global}, entropy, short-run emphasis (SRE), long-run emphasis (LRE), run-length non-uniformity (RLN), and run percentage (RP)] were

extracted for mid- (T5-T8) and lower thoracic (T9-T12), and lumbar vertebrae (L1-L5), respectively.



Steps of automated vertebral body segmentation, as performed by the convolutional neural network framework. From left to right: Automated vertebral body detection and labeling. Segmentation of vertebral components, including posterior elements (sagittal and coronal view). Separation of cortical and trabecular bone. Three-dimensional reconstruction of segmented vertebra [17].

SRE, LRE, RLN, and RP exhibited substantial reproducibility with RMSCV-values below 2%, for both sexes and at all spine levels, while vBMD was less reproducible (RMSCV = 11.9-16.2%). Thus, opportunistic assessment of texture features and vBMD in a single scanner environment using the presented CNN-based framework yields substantial reproducibility.

Fourth, we applied our automated framework in a cohort of 376 patients to characterize variations with regard to gender, age and vertebral level [13]. These gender-, age- and vertebral-level-specific values may serve as reference values for opportunistic osteoporosis diagnostics.

Fifth, we investigated the feasibility of using routine clinical MDCT scans for conducting FEM analysis to predict vertebral bone strength for opportunistic osteoporosis screening [14]. Routine abdominal MDCT with and without intravenous contrast medium and reconstructions with different sagittal slice thickness (1 and 3 mm, respectively) were used. The FEM-predicted failure loads obtained from routine MDCT scans were strongly correlated ($R^2 = 0.9$) with and without intravenous contrast medium and different slice thickness.

We also demonstrated in a pilot study of 16 subjects who sustained incidental osteoporotic vertebral fractures during image follow-up that FEM can predict incidental osteoporotic fractures at vertebral-specific level [20].

Sixth, we used the framework to compare BMD measurements derived from automatic and manual assessment in routine MDCT with DXA in their association with prevalent osteoporotic vertebral fractures [15]. All measures performed significantly better as predictors for vertebral fractures compared to DXA (e.g., AUC = 0.885 for trabecular vBMD and AUC = 0.86 for integral vBMD vs. AUC = 0.668 for DXA aBMD, respectively; both $p < 0.001$).

Sventh, we tried to establish and evaluate the diagnostic accuracy of volumetric BMD threshold values at different spinal levels, derived from clinical routine MDCT for the prediction of incident vertebral fractures (VF) [16]. In this case-control study, 35 incident VF cases (23 women, 12 men; mean age: 67 years) and 70 sex- and age-matched controls were included. Volumetric BMD at each single level of the thoracolumbar spine was significantly associated with incident VFs (odds ratio per SD decrease [OR], 95% confidence interval [CI] at T1-T4: 3.28, 1.66-6.49; at T5-T8: 3.28, 1.72-6.26; at T9-T12: 3.37, 1.78-6.36; and at L1-L4: 3.98, 1.97-8.06), independent of adjustment for age, sex, and prevalent VF. AUC showed no significant difference between vertebral levels and was highest at the thoracolumbar junction (AUC = 0.75, 95%-CI = 0.63 - 0.85 for T11-L2).

Lastly, we investigated the performance of BMD measurements based on our automated framework in vertebral osteoporotic fracture (VF) prediction as compared to fracture prevalence-based prediction models [17]. 420 patients (mean age, 63 years \pm 9, 276 males) were included in this study. Mean vBMD was calculated for levels T5-8, T9-12, and L1-5. Odds ratios (ORs) for prevalent and incident VFs were calculated for vBMD (per standard deviation decrease) at each level, for baseline VF prevalence (yes/no), and for baseline VF count (n) using logistic regression models, adjusted for age and sex. Models were compared using Akaike's and Bayesian information criteria (AIC & BIC). Individuals with lower vBMD at any spine level had higher odds for VFs (L1-5, prevalent VF: OR,95%-CI,p: 2.2, 1.4-3.5,p=0.001; incident VF: 3.5, 1.8-6.9,p<0.001). In contrast, VF status (2.15, 0.72-6.43,p=0.170) and count (1.38, 0.89-2.12,p=0.147) performed worse in incident VF prediction. Information criteria revealed best fit for vBMD-based models (AIC vBMD=165.2; VF status=181.0; count=180.7). Thus, VF prediction based on automatically extracted vBMD from routine clinical MDCT outperforms prediction models based on VF status and count. These findings underline the importance of opportunistic quantitative osteoporosis screening in clinical routine MDCT data.

4 Published Project Results

List of the ten most important publications related to this research project:

1. Long-term reproducibility of opportunistically assessed vertebral bone mineral density and texture features in routine clinical multi-detector computed tomography using an automated segmentation framework. Bodden J, Dieckmeyer M, Sollmann N, Rühling S, Prucker P, Löffler MT, Burian E, Subburaj K, Zimmer C, Kirschke JS, Baum T. **Quant Imaging Med Surg**. 2023 Sep 1;13(9):5472-5482. doi: 10.21037/qims-23-19. Epub 2023 Aug 9.
2. Incidental vertebral fracture prediction using neuronal network-based automatic spine segmentation and volumetric bone mineral density extraction from routine clinical CT scans. Bodden J, Dieckmeyer M, Sollmann N, Burian E, Rühling S, Löffler MT, Sekuboyina A, El Hussein M, Zimmer C, Kirschke JS, Baum T. **Front Endocrinol (Lausanne)**. 2023 Jul 17;14:1207949. doi: 10.3389/fendo.2023.1207949. eCollection 2023.
3. Level-Specific Volumetric BMD Threshold Values for the Prediction of Incident Vertebral Fractures Using Opportunistic QCT: A Case-Control Study. Dieckmeyer M, Löffler MT, El Hussein M, Sekuboyina A, Menze B, Sollmann N, Wostrack M, Zimmer C, Baum T, Kirschke JS. **Front Endocrinol (Lausanne)**. 2022 May 20;13:882163. doi: 10.3389/fendo.2022.882163. eCollection 2022.
4. Automated Opportunistic Osteoporosis Screening in Routine Computed Tomography of the Spine: Comparison With Dedicated Quantitative CT. Sollmann N, Löffler MT, El Hussein M, Sekuboyina A, Dieckmeyer M, Rühling S, Zimmer C, Menze B, Joseph GB, Baum T, Kirschke JS. **J Bone Miner Res**. 2022 Jul;37(7):1287-1296. doi: 10.1002/jbmr.4575. Epub 2022 Jun 15.
5. Gender-, Age- and Region-Specific Characterization of Vertebral Bone Microstructure Through Automated Segmentation and 3D Texture Analysis of Routine Abdominal CT. Dieckmeyer M, Sollmann N, El Hussein M, Sekuboyina A, Löffler MT, Zimmer C, Kirschke JS, Subburaj K, Baum T. **Front Endocrinol (Lausanne)**. 2022 Jan 27;12:792760. doi: 10.3389/fendo.2021.792760. eCollection 2021.
6. Automated detection of the contrast phase in MDCT by an artificial neural network improves the accuracy of opportunistic bone mineral density measurements. Rühling S, Navarro F, Sekuboyina A, El Hussein M, Baum T, Menze B, Braren R, Zimmer C, Kirschke JS. **Eur Radiol**. 2022 Mar;32(3):1465-1474. doi: 10.1007/s00330-021-08284-z. Epub 2021 Oct 23.
7. Predicting Vertebral Bone Strength Using Finite Element Analysis for Opportunistic Osteoporosis Screening in Routine Multidetector Computed Tomography Scans-A Feasibility Study. Rayudu NM, Dieckmeyer M, Löffler MT, Noël PB, Kirschke JS, Baum T, Subburaj K. **Front Endocrinol (Lausanne)**. 2021 Jan 19;11:526332. doi: 10.3389/fendo.2020.526332. eCollection 2020.
8. Automatic opportunistic osteoporosis screening in routine CT: improved prediction of patients with prevalent vertebral fractures compared to DXA. Löffler MT, Jacob A, Scharf A, Sollmann N, Burian E, El Hussein M, Sekuboyina A, Tetteh G, Zimmer C, Gempt J, Baum T, Kirschke JS. **Eur Radiol**. 2021 Aug;31(8):6069-6077. doi: 10.1007/s00330-020-07655-2. Epub 2021 Jan 28.
9. Spectral-detector based x-ray absorptiometry (SDXA): in-vivo bone mineral density measurements in patients with and without osteoporotic fractures. Laugerette A, Baum T, Gersing AS, Schwaiger BJ, Brown K, Frerking LC, Shapira N, Pfeiffer D, Rummeny EJ, Proksa R, Pfeiffer F, Noël PB. **Biomed Phys Eng Express**. 2020 Sep 8;6(5):055021. doi: 10.1088/2057-1976/abab6b.

10. Opportunistic osteoporosis screening: contrast-enhanced dual-layer spectral CT provides accurate measurements of vertebral bone mineral density. Roski F, Hammel J, Mei K, Haller B, Baum T, Kirschke JS, Pfeiffer D, Woertler K, Pfeiffer F, Noël PB, Gersing AS, Schwaiger BJ. **Eur Radiol.** 2021 May;31(5):3147-3155. doi: 10.1007/s00330-020-07319-1. Epub 2020 Oct 14.

5 Further information on the project, qualifications and outlook

5.1 Doctoral researchers involved:

Doctoral researchers	Gender (m/f/d)	Doctoral status (ongoing, finished, discontinued)	Start and (where applicable) finish of doctoral studies:	Funding within the framework of the project
Dr. Nico Sollmann	M	Habilitation	Completed 2021	2020-2022
Dr. Michael Dieckmeyer	M	Habilitation	Completed 2022	2020-2022
Ferdinand Roski	M	Promotion Dr. med	Completed 2022	
Florian Zoffl	M	Promotion Dr. med	Completed 2023	
Eduardo Becherucci	M	Promotion Dr. med	Completed 2023	

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- Schuit, S.C., et al., *Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study*. Bone, 2004. **34**(1): p. 195-202.
- Keaveny, T.M., et al., *Biomechanical Computed Tomography analysis (BCT) for clinical assessment of osteoporosis*. Osteoporos Int, 2020. **31**(6): p. 1025-1048.
- Leonhardt, Y., et al., *Opportunistic QCT Bone Mineral Density Measurements Predicting Osteoporotic Fractures: A Use Case in a Prospective Clinical Cohort*. Front Endocrinol (Lausanne), 2020. **11**: p. 586352.
- Rayudu, N.M., et al., *Finite Element Analysis-Based Vertebral Bone Strength Prediction Using MDCT Data: How Low Can We Go?* Front Endocrinol (Lausanne), 2020. **11**: p. 442.
- Burian, E., et al., *Low-dose MDCT: evaluation of the impact of systematic tube current reduction and sparse sampling on quantitative paraspinous muscle assessment*. Quant Imaging Med Surg, 2021. **11**(7): p. 3042-3050.

7. Sollmann, N., et al., *Low-dose MDCT: evaluation of the impact of systematic tube current reduction and sparse sampling on the detection of degenerative spine diseases*. *Eur Radiol*, 2021. **31**(4): p. 2590-2600.
8. Sollmann, N., et al., *Low-Dose MDCT of Patients With Spinal Instrumentation Using Sparse Sampling: Impact on Metal Artifacts*. *AJR Am J Roentgenol*, 2021. **216**(5): p. 1308-1317.
9. Laugerette, A., et al., *Spectral-detector based x-ray absorptiometry (SDXA): in-vivo bone mineral density measurements in patients with and without osteoporotic fractures*. *Biomed Phys Eng Express*, 2020. **6**(5): p. 055021.
10. Roski, F., et al., *Opportunistic osteoporosis screening: contrast-enhanced dual-layer spectral CT provides accurate measurements of vertebral bone mineral density*. *Eur Radiol*, 2021. **31**(5): p. 3147-3155.
11. Sollmann, N., et al., *Automated Opportunistic Osteoporosis Screening in Routine Computed Tomography of the Spine: Comparison With Dedicated Quantitative CT*. *J Bone Miner Res*, 2022. **37**(7): p. 1287-1296.
12. Bodden, J., et al., *Long-term reproducibility of opportunistically assessed vertebral bone mineral density and texture features in routine clinical multi-detector computed tomography using an automated segmentation framework*. *Quant Imaging Med Surg*, 2023. **13**(9): p. 5472-5482.
13. Dieckmeyer, M., et al., *Gender-, Age- and Region-Specific Characterization of Vertebral Bone Microstructure Through Automated Segmentation and 3D Texture Analysis of Routine Abdominal CT*. *Front Endocrinol (Lausanne)*, 2021. **12**: p. 792760.
14. Rayudu, N.M., et al., *Predicting Vertebral Bone Strength Using Finite Element Analysis for Opportunistic Osteoporosis Screening in Routine Multidetector Computed Tomography Scans- A Feasibility Study*. *Front Endocrinol (Lausanne)*, 2020. **11**: p. 526332.
15. Loffler, M.T., et al., *Automatic opportunistic osteoporosis screening in routine CT: improved prediction of patients with prevalent vertebral fractures compared to DXA*. *Eur Radiol*, 2021. **31**(8): p. 6069-6077.
16. Dieckmeyer, M., et al., *Level-Specific Volumetric BMD Threshold Values for the Prediction of Incident Vertebral Fractures Using Opportunistic QCT: A Case-Control Study*. *Front Endocrinol (Lausanne)*, 2022. **13**: p. 882163.
17. Bodden, J., et al., *Incidental vertebral fracture prediction using neuronal network-based automatic spine segmentation and volumetric bone mineral density extraction from routine clinical CT scans*. *Front Endocrinol (Lausanne)*, 2023. **14**: p. 1207949.
18. Rayudu, N.M., et al., *Low-dose and sparse sampling MDCT-based femoral bone strength prediction using finite element analysis*. *Arch Osteoporos*, 2020. **15**(1): p. 17.
19. Ruhling, S., et al., *Automated detection of the contrast phase in MDCT by an artificial neural network improves the accuracy of opportunistic bone mineral density measurements*. *Eur Radiol*, 2022. **32**(3): p. 1465-1474.
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