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Osteoporosis is a disease characterized by loss of bone mass and structural deterioration leading to increased risk of fracture. Currently, osteoporosis is diagnosed by measurement of areal bone mineral density by dualenergy x-ray absorptiometry (DXA). However, the majority of fractures occur in both women and men who are not classified as osteoporotic by current DXA criteria (T-score ≤ -2.5). As a 2-dimensional (2D) technology, DXA does not provide information about 3-dimensional (3D) bone structure, shape and geometry, which substantially contribute to bone strength and resistance to fracture. Finite element (FE) analysis of quantitative computed tomography (QCT) images can provide 3D structure and strength measurements but QCT is impractical for widespread clinical use because of high radiation exposure and expense. In contrast, DXA is widely available, inexpensive and has low radiation exposure. What is needed is a method by which DXA images can be used to generate 3D shape models that incorporate bone structure and geometry. However, fractures are complex events influenced by other factors including age, race, body mass index, risk of falls, and prior medical and fracture history. Even sophisticated measurements of bone density, structure, and strength may not be able to predict fractures accurately. Machine learning is an emerging field in which models are created by "learning" from previous data. These models can incorporate various factors and be used to classify or predict outcomes for new data. The overall hypothesis of this proposal is that advanced analyses of widely available DXA images that incorporate structural and strength information and statistical modeling using machine learning to incorporate additional risk factors will better identify patients at high risk of osteoporotic fracture. This hypothesis will be tested using QCT and DXA data from previous studies to generate 3D statistical shape models that describe variability in proximal femur morphology. By aligning 2D DXA images to the models, patient-specific 3D models will be reconstructed for quantitative analyses and combined with FE analysis to estimate bone strength. Machine learning models will be used to incorporate these novel measurements, demographics, and various risk factors for fracture to predict incident fractures in two very large, prospective studies. The ultimate goal of this proposal is to increase the diagnostic utility of DXA, a safe, non-invasive, and widely available technology, by applying novel image processing and statistical techniques to predict fractures more accurately.