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Administrative healthcare data applied to fracture risk assessment

S. Yang[1] · W.D. Leslie[2] · S.N. Morin[3] · L.M. Lix[4]

Abstract

Summary Fracture risk scores generated from population-based administrative healthcare data showed comparable or better discrimination than the Fracture Risk Assessment Tool (FRAX) scores computed without bone mineral density for predicting incident major osteoporotic fracture. Administrative data may be useful to identify individuals at high fracture risk at the population level.

Purpose To evaluate the discrimination of fracture risk scores defined using inputs available from administrative data for predicting incident major osteoporotic fracture (MOF) and hip fracture (HF) alone.

Methods Using the Manitoba Bone Mineral Density (BMD) Database (1997–2013), we identified 61,041 individuals aged 50 years or older with healthcare coverage following their first BMD test. We calculated two-modified FRAX)scores based on administrative data: FRAX-A and FRAX-A$^+$. The FRAX-A modification used all FRAX inputs, except for BMD, body mass index, and parental HF, while the FRAX-A$^+$ modification using all FRAX-A inputs plus a comorbidity score, number of hospitalizations in the 3 years prior to the BMD test, depression diagnosis, and dementia diagnosis. FRAX scores computed with BMD (i.e., FRAX [BMD]) and without BMD (i.e., FRAX [no-BMD]) were the comparators.

Results During a mean of 7 years of follow-up, we identified 5306 (8.7%) incident MOF and 1532 (2.5%) incident HF. The c-statistic for MOF associated with FRAX-A was lower than FRAX (BMD) (0.655 vs 0.675; $P < 0.05$) and comparable to FRAX (no-BMD) (0.654; $P = 0.07$). The c-statistic for MOF using FRAX-A$^+$ (0.663) was lower than FRAX (BMD) but higher than FRAX (no-BMD) (both $P < 0.05$). For predicting incident HF, c-statistics associated with FRAX-A (0.762) and FRAX-A$^+$ (0.767) were lower than FRAX (BMD) (0.789) and FRAX (no-BMD) (0.773; both $P < 0.05$).

Conclusions FRAX-A and FRAX-A$^+$ showed comparable or better discrimination than FRAX without BMD for predicting incident MOF, but slightly lower discrimination for HF alone.

Keywords Administrative data · Fracture risk · FRAX · Osteoporosis · Risk assessment

✉ S. Yang
shumanyang@jlu.edu.cn

✉ W.D. Leslie
bleslie@sbgh.mb.ca

1 Department of Epidemiology and Biostatistics, School of Public Health, Jilin University, 232-1163 Xinmin Street, Changchun 130021, Jilin, China

2 Department of Internal Medicine, University of Manitoba, C5121-409 Tache Ave, Winnipeg, Manitoba R2H 2A6, Canada

3 Department of Medicine, McGill University, Montreal, Quebec, Canada

4 Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

Introduction

Osteoporosis and osteoporotic fracture are major public health problems because they are highly prevalent among the elderly and lead to substantial healthcare costs, morbidity, increased risk of institutionalization and mortality [1–4]. Accurate assessment of osteoporosis-related fracture risk is a prerequisite to addressing these problems.

The most commonly used and internationally validated fracture risk prediction algorithm is the fracture risk assessment tool (FRAX), which estimates the absolute probability of a major osteoporotic fracture (MOF, comprising hip, clinical vertebral, forearm, or humerus) or hip fracture (HF) for an individual in the next 10 years [5, 6]. FRAX uses the following independent risk factors: age, sex, body mass index (BMI), prior history of fracture, parental HF, current smoking, prolonged glucocorticoid use, rheumatoid arthritis, secondary

osteoporosis, alcohol intake 3 or more units/day and, optionally, femoral neck bone mineral density (BMD) [5, 6]. Population-based screening to identify high fracture risk using FRAX in the SCOOP trial was effective at preventing HF outcomes, though a significant effect was not seen for the primary outcome of all osteoporosis-related fractures [7].

Many studies have investigated the discrimination of FRAX with or without BMD for assessing individual fracture risk [8–10]. However, few studies [11, 12] have assessed the comparative discrimination of fracture risk scores limited to information routinely available in population-based healthcare administrative data, in which BMD, BMI, and parental HF are typically not available. If a fracture risk score calculated from administrative data could be validated to identify high-risk individuals, then it may be feasible to apply this for population screening, supporting targeted BMD testing and/or personalized fracture prevention strategies. This is a potentially cost-effective approach to target limited healthcare resources towards individuals with a high risk of fracture. Thus, the aim of the current study was to test the discrimination of fracture risk scores generated only from information available in population-based healthcare administrative data for predicting incident MOF or HF alone.

Methods

Study population

The Manitoba Bone Mineral Density Database (MBMDD) for the province of Manitoba, Canada is a population-based registry of clinical DXA results [13, 14]. The MBMDD has been linked with patient demographics, clinical data, relevant diagnoses from hospitalizations and physician visits, and prescription drug dispensation records.

Using the MBMDD from April 1, 1997 to March 31, 2013, we identified all individuals aged 50 years or older at their first BMD test. We excluded individuals without provincial healthcare coverage following their first BMD test.

Generation of fracture risk scores

FRAX inputs were derived from a combination of self-report, measured, registry and administrative data. Body weight and height were self-reported prior to 2000 (10.5% of the study sample) and measured from 2000 onwards. BMI was calculated as body weight (kg) divided by the square of body height (m^2). Prior fractures were ascertained from hospital records and/or physician visit claims using validated definitions from 1987 until the date of the BMD test [15, 16]. Parental HF was ascertained from a structured self-reported questionnaire from 2005 onwards; missing data were considered "not present" in our study (46.4% of the study sample). Chronic obstructive

pulmonary disease (COPD), alcohol/substance abuse and rheumatoid arthritis diagnoses were based on at least one hospital record or two-physician visit claims with a relevant diagnosis during the 3 years prior to the BMD test. COPD and alcohol/substance abuse diagnoses from administrative data are proxy measures for smoking and high alcohol intake, respectively [17, 18]. Prolonged glucocorticoid use ($\geq$ 3 months in the year prior to the BMD test) was captured in the province-wide retail pharmacy database system. Data on femoral neck T-scores were derived from cross-calibrated DXA scans (DPX, Prodigy or iDXA, GE Healthcare). Secondary osteoporosis was defined using the following diseases during the 3 years prior to the BMD test (at least one hospital record or two-physician visit claims with a relevant diagnosis): hyperthyroidism, chronic malnutrition, chronic liver disease, inflammatory bowel disease, Parkinson's disease, cerebrovascular disease, multiple sclerosis, ankylosing spondylitis, and organ transplant. Hospitalization since 1987 with a relevant procedure code was used for ascertaining organ transplant.

We generated two FRAX and three modified FRAX scores for MOF and HF outcomes using the Canadian FRAX tool (FRAX® Desktop Multi-Patient Entry, version 3.7): FRAX (BMD), FRAX (no-BMD), FRAX (age-sex-fracture), FRAX (age-sex), and FRAX-A. The inputs used to calculate each score are shown in Supplemental Table 1. FRAX (BMD) and FRAX (no-BMD) refer to fracture probability calculated using all FRAX inputs with and without BMD, respectively and served as the reference comparators. FRAX (BMD) provides the upper bound discrimination while FRAX (no-BMD) is the most relevant comparator for population-based screening methods without BMD. To define the lower bound discrimination from minimal models, we calculated FRAX (age-sex-fracture) and FRAX (age-sex) using age, sex and prior fracture information only. For calculating FRAX (age-sex-fracture), we assumed 27 kg/m^2 for BMI (the mean for our cohort) and "not present" for binary FRAX inputs other than prior fracture. FRAX (age-sex) was calculated similarly but with coding prior fracture as "not present". In calculating FRAX-A, we assumed 27 kg/m^2 for BMI, "not present" for parental HF and the actual data for all other FRAX inputs. To correct for the miscalibration created by systematically excluding risk factor information, we applied age- and sex-specific ratio adjustments to FRAX (age-sex), FRAX (age-sex-fracture), FRAX-A to provide calibration equal to FRAX (BMD); ratios were calculated using the medians of fracture scores in each age- and sex-specific group.

To investigate the possibility of improving the discrimination of FRAX-A for assessing fracture risk, we derived FRAX-A$^+$ from the inputs used for calculating FRAX-A plus additional non-FRAX inputs (Supplemental Table 1). Again, we assumed 27 kg/m^2 for BMI, "not present" for parental HF for calculating FRAX-A$^+$. The selection of non-FRAX inputs was based on the following criteria: (1) available in

administrative data and (2) showed an independent association with incident MOF in multivariable models. Aggregated Diagnostic Group (ADG) scores, an index of comorbidities for predicting mortality, were calculated using the Johns Hopkins Adjusted Clinical Group ® (ACG®) Case-Mix System (version 9). Depression and dementia diagnoses were ascertained based on at least one hospital record or two physician visits with a relevant diagnosis during the 3 years prior to the BMD test. Because FRAX-A$^+$ cannot be calculated using the FRAX tool, we used multivariable survival regression analysis adjusting for the competing risk of death for calculating an individuals' 10-year risk of MOF and HF alone [19]. Again, we applied age- and sex-specific ratio adjustments to FRAX-A$^+$ to give equal calibration to FRAX (BMD).

Ascertainment of incident fractures

Incident MOF (hip, forearm, clinical spine, or humerus fracture) were ascertained from relevant International Classification of Diseases (ICD) codes in hospital records (the data source for HF diagnosis) and physician visit claims (an additional source for forearm, clinical spine or humerus fracture diagnosis) using validated case definitions [15, 16]; ICD-9-Clinical Modification (CM) was used before 2004; ICD-10-Canadian Adaptation (CA) was used from 2004 onwards. We excluded any incident fracture associated with high-trauma ICD codes. Rates of MOF identified from these case definitions are concordant with those from the population-based Canadian Multicentre Osteoporosis Study (CaMos) [15], in which MOF was ascertained from x-ray and clinical records. Follow-up was censored at death, out-of-province migration or end of the study period (March 31, 2013), whichever came first.

Statistical analysis

We descriptively analyzed the individual FRAX risk factors, FRAX (BMD) for MOF and HF alone, and non-FRAX risk factors in the entire cohort, and then separately in those with and without incident MOF. Categorical variables are shown as percentages; fracture risk scores are shown as medians (interquartile ranges); other data are shown as means (SDs).

We used multivariable Cox proportional hazard models to test the associations of all factors included in the FRAX-A$^+$ calculation with incident MOF and HF alone. In addition, we computed the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incident MOF and HF alone associated with each risk score (per SD increase). All risk scores were log transformed to correct for a skewed distribution.

The Brier score was used to assess model calibration and prediction accuracy for the risk scores [20]. The Brier score measures the accuracy of probabilistic prediction models for assessing the risk of categorical outcomes [20]. Brier scores can range from zero to one; a lower score indicates better model calibration and prediction accuracy. In addition, we calculated c-statistics and 95% CIs for incident MOF and HF alone using logistic regression models associated with FRAX-A and FRAX-A$^+$, FRAX (BMD), FRAX (no-BMD), FRAX (age-sex-fracture), and FRAX (age-sex). Differences in c-statistics were tested using the method of Delong et al. [21]. The comparison was based upon the null hypothesis of equal c-statistics (i.e., superiority testing). All analyses were performed with SAS (Version 9.4, SAS Institute Inc., Cary, NC) and R (Version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 61,041 eligible individuals for analysis. The average age was 66.3 years (SD 9.8 years) and 90.8% were female. There were 13.9% and 3.6% individuals censored due to death or out-of-province migration, respectively.

During a mean of 7 years of follow-up, we identified 5306 (8.7%) incident MOF and 1532 (2.5%) incident HF. Except for parental HF, all other FRAX risk factors followed expected trends in individuals with MOF (e.g., older age, higher percent of female, prior fracture, COPD diagnosis, rheumatoid arthritis diagnosis, secondary osteoporosis, alcohol/substance abuse, and prolonged glucocorticoid use, lower BMI, and femoral neck T-score) as compared to those without incident MOF (Table 1). Individuals with incident MOF also had significantly higher ADG scores, greater numbers of hospitalizations, and were significantly more likely to have depression and dementia diagnoses than those without incident MOF (Table 1). In the Cox proportional hazard model, except for prolonged glucocorticoid use, all other factors included in the FRAX-A$^+$ calculation were significantly associated with incident MOF (Supplemental Table 2). Except for ADG score 3–5 vs ≤ 2, all other factors included in the FRAX-A$^+$ model were significantly associated with incident HF.

HRs for incident MOF and incident HF alone associated with FRAX (BMD), FRAX (no-BMD), FRAX (age-sex-fracture), FRAX (age-sex), FRAX-A, and FRAX-A$^+$ were all statistically significant; HRs for MOF were consistently lower than those for HF (Table 2). We found similar sex-stratified associations of all risk scores with incident MOF and HF. The Brier scores for all risk scores for incident MOF and HF were all < 0.01, indicating an excellent calibration of the prediction models (Supplemental Table 3). Similar results were noted when the analyses were stratified by sex.

As expected, the highest c-statistics in the overall population was for FRAX (BMD) and the lowest was for FRAX (age-sex). The c-statistic for incident MOF associated with FRAX-A was lower than for FRAX (BMD) and FRAX-A$^+$

Table 1 Baseline characteristics of the study cohort stratified by incident major osteoporotic fracture (MOF)

Variable	All cohort members $N = 61{,}041$	Cohort members with incident MOF $N = 5306$	Cohort members without incident MOF $N = 55{,}735$
FRAX inputs			
Age (years)	66.3 (9.8)	70.4 (10.0)	66.0 (9.7)**
Body mass index (kg/m^2)	27.2 (5.4)	26.1 (5.0)	27.3 (5.4)**
Femoral neck T-score	−1.3 (1.1)	−1.9 (1.0)	−1.3 (1.1)**
Female (%)	90.8	93.2	90.5**
Prior fracture (%)	14.7	25.6	13.7**
Parental hip fracture (%)	6.3	3.3	6.6
COPD diagnosis (smoking proxy, %)	8.9	11.9	8.6**
Rheumatoid arthritis diagnosis (%)	3.4	5.1	3.2**
Secondary osteoporosis (%)	10.9	13.7	10.7**
Alcohol/substance abuse (high alcohol use proxy, %)	1.3	2.3	1.2**
Prolonged glucocorticoid use (%)	5.0	6.1	4.9**
FRAX(BMD) for MOF	8.0 (5.4, 12.7)	12.0 (7.7, 18.8)	7.7 (5.3, 12.2)**
FRAX(BMD) for hip fracture	1.0 (0.3, 2.9)	2.6 (0.9, 6.2)	0.9 (0.3, 2.6)**
Non-FRAX inputs			
Aggregated diagnostic groups score (%)			
≤ 2	19.6	13.6	20.2**
3–5	44.7	41.7	45.0**
6+	35.7	44.7	34.8**
Hospitalizations, 3 years prior to BMD test (%)			
0	74.6	67.1	75.4**
1	15.8	18.8	15.5**
2+	9.6	14.1	9.1**
Depression diagnosis (%)	10.4	12.1	10.2**
Dementia diagnosis (%)	1.0	2.2	0.9**

COPD, chronic obstructive pulmonary disease. Unless otherwise specified, FRAX scores are shown as medians (interquartile ranges) and other data are shown as means (SDs)

**Indicates statistically significant difference at $\alpha = 0.01$ for individuals with and without incident MOF

(0.655 vs 0.675 and 0.663, respectively; both $P < 0.05$; Table 3), and was comparable to FRAX (no-BMD) (0.654; $P = 0.07$). The c-statistic for MOF associated with FRAX-A$^+$ (0.663) was lower than FRAX (BMD) (0.675), and higher than FRAX (no-BMD) (0.654; both $P < 0.05$). For predicting incident HF, we found c-statistics associated with FRAX-A and FRAX-A$^+$ were lower than FRAX (BMD) and FRAX (no-BMD). For predicting MOF and HF; the c-statistics for FRAX-A and FRAX-A$^+$ were significantly greater than for the minimal models, FRAX (age-sex-fracture) and FRAX (age-sex) (all $P < 0.05$). In the sex-stratified analysis for predicting MOF and HF, the c-statistics for FRAX-A and FRAX-A$^+$ were higher in females than in males (all $P < 0.05$). In either sex, FRAX-A and FRAX (no-BMD) showed comparable c-statistics for MOF, but the c-statistic for HF from FRAX-A was lower than FRAX (no-BMD). MOF c-statistics for FRAX-A+ were significantly greater than for FRAX (no-BMD) in both males and females, while HF c-statistics were not significantly different.

Discussion

In this large cohort study, we demonstrated the potential usefulness of fracture risk scores generated only from information available in population-based healthcare administrative data. As expected, FRAX (BMD) gave better discrimination than methods that did not include BMD. Of greater relevance for population-based screening without BMD, FRAX-A showed measures of MOF stratification comparable to FRAX (no-BMD), and only slightly lower for HF risk stratification (not significant in sex-stratified analyses). FRAX-A$^+$ was worse than FRAX (BMD) but better than FRAX (no-BMD) for predicting incident MOF. Although FRAX (age-sex-fracture) and FRAX (age-sex) are much easier to be calculated and used, they gave worse discrimination than FRAX-A and FRAX-A$^+$ for stratifying MOF risk. In the sex-stratified analyses, the discrimination of FRAX-A and FRAX-A$^+$ for predicting MOF and HF alone was better in females than in males. However, in either sex, FRAX-A and FRAX-A$^+$ showed comparable or better discrimination than FRAX (no-BMD) for predicting MOF.

Reber et al. [11] studied the discrimination of fracture risk assessment using insurance claims data from one health insurance company (in a German agricultural population aged 65 years and older) and demonstrated that administrative data could be used to predict incident MOF. They also reported that adding other risk factors to age, sex, and prior fracture showed an improvement in fracture risk assessment. These results are consistent with the results of our study. Another Danish

Table 2 Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incident major osteoporotic fracture (MOF) and incident hip fracture associated with each risk score (per SD increase), stratified by sex

Variable	Male		Female		Overall	
	MOF	Hip fracture	MOF	Hip fracture	MOF	Hip fracture
FRAX (BMD)	1.83 (1.66, 2.01)	3.35 (2.60, 4.30)	1.99 (1.94, 2.05)	4.22 (3.93, 4.53)	1.98 (1.93, 2.03)	4.22 (3.93, 4.52)
FRAX (no-BMD)	1.71 (1.54, 1.90)	2.53 (2.01, 3.19)	1.91 (1.85, 1.96)	3.63 (3.40, 3.88)	1.88 (1.83, 1.93)	3.54 (3.32, 3.76)
FRAX (age-sex-fracture)	1.74 (1.57, 1.92)	2.44 (1.92, 3.11)	1.83 (1.78, 1.88)	3.38 (3.16, 3.61)	1.82 (1.77, 1.87)	3.38 (3.17, 3.61)
FRAX (age-sex)	1.53 (1.37, 1.72)	2.43 (1.92, 3.09)	1.74 (1.69, 1.79)	3.25 (3.05, 3.47)	1.72 (1.67, 1.77)	3.27 (3.06, 3.48)
FRAX-A	1.62 (1.47, 1.80)	2.15 (1.72, 2.69)	1.91 (1.87, 1.97)	3.43 (3.22, 3.65)	1.89 (1.84, 1.94)	3.40 (3.19, 3.62)
FRAX-A[+]	1.81 (1.63, 1.98)	2.54 (2.05, 3.14)	1.92 (1.87, 1.98)	3.47 (3.26, 3.69)	1.92 (1.87, 1.97)	3.47 (3.27, 3.69)

All fracture probabilities were evaluated on the logarithmic scale. All HRs are statistically significant at $\alpha = 0.05$

Table 3 c-statistics and 95% confidence intervals for incident major osteoporotic fracture (MOF) and incident hip fracture alone, stratified by sex

Variable	Male		Female		Overall	
	MOF	Hip fracture	MOF	Hip fracture	MOF	Hip fracture
FRAX (BMD)	0.681 (0.654, 0.707)[a,b]	0.764 (0.722, 0.806)[a,b]	0.673 (0.665, 0.681)[a,b]	0.793 (0.782, 0.804)[a,b]	0.675 (0.667, 0.682)[a,b]	0.789 (0.779, 0.800)[a,b]
FRAX (no-BMD)	0.618 (0.589, 0.648)[b]	0.674 (0.625, 0.723)[a]	0.655 (0.646, 0.663)[b]	0.779 (0.768, 0.790)[a]	0.654 (0.646, 0.662)[b]	0.773 (0.762, 0.784)[a,b]
FRAX (age-sex-fracture)	0.624 (0.594, 0.654)	0.657 (0.605, 0.709)	0.649 (0.641, 0.657)[a,b]	0.762 (0.750, 0.774)[a,b]	0.649 (0.641, 0.657)[a,b]	0.755 (0.743, 0.766)[a,b]
FRAX (age-sex)	0.584 (0.553, 0.615)[a,b]	0.663 (0.612, 0.714)	0.632 (0.624, 0.641)[a,b]	0.756 (0.744, 0.768)[a,b]	0.631 (0.623, 0.639)[a,b]	0.749 (0.738, 0.761)[a,b]
FRAX-A	0.616 (0.586, 0.646)	0.648 (0.598, 0.698)	0.656 (0.648, 0.664)	0.770 (0.759, 0.782)	0.655 (0.647, 0.663)	0.762 (0.751, 0.773)
FRAX-A[+]	0.648 (0.619, 0.677)[a]	0.676 (0.626, 0.727)[a]	0.663 (0.655, 0.671)[a]	0.775 (0.763, 0.786)[a]	0.663 (0.655, 0.671)[a]	0.767 (0.756, 0.778)[a]

[a] Indicates statistically significant difference at $\alpha = 0.05$ when compared to FRAX-A

[b] Indicates statistically significant at $\alpha = 0.05$ when compared to FRAX-A[+]

nationwide population- and register-based cohort study [12] also developed and tested a fracture prediction model using administrative data; it showed good accuracy for identifying high MOF (*c*-statistics = 0.750 and 0.752 for females and males, respectively) and HF (*c*-statistics = 0.874 and 0.851 for females and males, respectively) risk individuals. In contrast with our study, this Danish study [12] found higher *c*-statistic in females than males for predicting HF, but not for predicting MOF. This may be due to the fact that different risk factors were included in predicting MOF in females (38 risk factors) and males (43 risk factors) in this Danish study [12]. The *c*-statistics in this Danish study [12] is higher than that in our study. This is likely due to two reasons: First, the Danish study [12] included many more risk factors than our study. However, it should be noted that some risk factors included in the Danish study [12] do not have a biologic relationship with fracture events, though they improved fracture prediction accuracy. Second, the Danish study [12] included a much larger number of younger subjects than our study population and showed that discrimination varied as a function of age (higher *c*-statistics in younger versus older subjects). For the age 65–69 years subgroup from the Danish study [12] and our study (mean age = 66.3 years old), *c*-statistics were comparable.

The effectiveness of FRAX scores to screen for high fracture risk individuals and prevent future fractures had been evaluated in several studies, but scores were calculated using the data collected through mailed questionnaires [22, 23]. As noted by Rubin et al. [23] and Rothmann et al. [24], responders to the mailed questionnaires tended to be younger, have higher social-economic status, and fewer comorbidities than non-responders, which created non-participation bias and higher fracture risk individuals were more likely to be missing from this screening process. Identifying high fracture risk individuals using administrative data does not have such issue; this may be a better surveillance system to identify high fracture risk individuals in a large population.

We acknowledge several limitations of the present study. First, 99% of our study population was Caucasian; we were unable to determine if ethnicity influenced the results. Second, in earlier years, we did not have data on self-reported parental HF; percents of parental HF between individuals with and without incident MOF were insignificant. Previously, we have shown that objectively verified parental HF ascertained from administrative data is independently associated with increased risk of incident fractures [25]. This creates an opportunity of replacing our current self-reported parental HF with objectively verified parental HF. Third, we tested the usefulness of a small number of non-FRAX risk factors (e.g., ADG scores, number of hospitalizations in the last 3 years prior to the BMD test, depression diagnoses, dementia diagnoses). Although including fewer risk factors may lead to worse discrimination, this will be easier to apply to the real practice. Lastly, FRAX-

A+ was developed and tested in the same study population and has not been externally validated; discrimination for predicting fractures may be better than would be seen in an independent study population.

In summary, FRAX-A and FRAX-A+ showed comparable or better discrimination than FRAX scores computed without BMD to stratify MOF fracture risk. Future studies are warranted to confirm that these algorithms can be deployed at the population level to identify high fracture risk individuals for targeted BMD testing and/or fracture prevention.

Compliance with ethical standards

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