Osteoporosis International
https://doi.org/10.1007/s00198-020-05588-6

ORIGINAL ARTICLE

# Vertebral fracture assessment (VFA) for osteoporosis screening in US postmenopausal women: is it cost-effective?

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Received: 4 June 2020 / Accepted: 4 August 2020
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## Abstract

**Summary** Vertebral fracture assessment (VFA) is cost-effective when it was incorporated in the routine screening for osteoporosis in community-dwelling women aged ≥ 65 years, which support guidelines, such as the National Osteoporosis Foundation (NOF) for the diagnostic use of VFA as an important addition to fracture risk assessment.

**Introduction** To evaluate the cost-effectiveness of VFA as a screening tool to reduce future fracture risk in US community–dwelling women aged ≥ 65 years.

**Methods** An individual-level state-transition cost-effectiveness model from a healthcare perspective was constructed using derived data from published literature. The time horizon was lifetime. Five screening strategies were compared, including no screening at all, central dual-energy X-ray absorptiometry (DXA) only, VFA only, central DXA followed by VFA if the femoral neck T-score (FN-T) ≤ − 1.5, or if the FN-T ≤ − 1.0. Various initiation ages and rescreening intervals were evaluated. Oral bisphosphonate treatment for 5-year periods was assumed. Incremental cost-effectiveness ratios (2017 US dollars per quality-adjusted life-year (QALY) gained) were used as the outcome measure.

**Results** The incorporation of VFA slightly increased life expectancy by 0.1 years and reduced the number of subsequent osteoporotic fractures by 3.7% and 7.7% compared with using DXA alone and no screening, respectively, leading to approximately 30 billion dollars saved. Regardless of initiation ages and rescreening intervals, central DXA followed by VFA if the FN-T ≤ − 1.0 was most cost-effective ($40,792 per QALY when the screening is initiated at age 65 years and with rescreening every 5 years). Results were robust to change in VF incidence and medication costs.

**Conclusion** In women aged ≥ 65 years, VFA is cost-effective when it was incorporated in routine screening for osteoporosis. Our findings support the National Osteoporosis Foundation (NOF) guidelines for the diagnostic use of VFA as an important addition to fracture risk assessment.

**Keywords** Cost-effectiveness · Osteoporosis · Postmenopausal women · Vertebral fracture · Vertebral fracture assessment

## Introduction

Vertebral fractures (VFs) are a hallmark of osteoporosis-related fractures, responsible for increased morbidity and mortality, and decreased quality of life. Updated data from the National Health and Nutrition Examination Survey (NHANES) have shown that the prevalence of VFs increased with age from < 5% in those < 60 to 11% in those 70–79 and

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Published online: 11 August 2020

16–21% in those ≥ 80 years [1]. In postmenopausal women, the risk of osteoporotic fractures doubles every 7–8 years [2]. In particular, the risk of VFs in women is elevated as compared with men with increasing risk with increasing age [3–5].

Prevalent VF is a major risk factor for subsequent fractures in untreated patients. It was reported that more than half of the patients with hip fracture had evidence of an existing VF and 14% had at least one severe VF[6]. A pooled analysis of the placebo group of 4 large randomized clinical trials (RCTs) found that presence of ≥ 1 VFs increased risk of experiencing a new VF within a year by fivefold compared with the incidence in individuals without prevalent VFs [7]. The highest incidence of subsequent fractures has been seen among women with both low bone mineral density (BMD) and ≥ 2 prevalent VFs, resulting in an increased risk of 75-fold, relative to women with normal bone mass and no existing VFs [8].

Despite the crucial role of VF identification of persons at high risk for fracture, VFs remain underdiagnosed and undertreated. More than two-thirds of patients with asymptomatic VFs never come to medical attention, and are diagnosed incidentally [9–11]; of those VFs that are clinically recognized, only 12.9% of their BMD are evaluated and 28.5% treated for the underlying disease of osteoporosis [12]. However, the vast majority of VFs cannot be recognized without proactive screening in individuals being assessed for osteoporosis. Traditionally, conventional X-rays of the thoracolumbar spine are considered to be the most accurate way to identify and confirm the presence of VFs. However, dual-energy X-ray absorptiometry (DXA) scanning of the entire spine for vertebral fracture assessment (VFA) is an emerging potential alternative to X-rays for VF detection [13, 14]. VFA only adds a few minutes to the time needed to perform BMD measurement [15]. The strengths of VFA over conventional X-rays are its minimal radiation exposure and low cost [15, 16].

Whether VFA should become a standard for screening in women at risk for osteoporosis relates to the fact that a high proportion of women with asymptomatic VFs have BMD levels that would not warrant treatment based on BMD alone [17]. The diagnosis of VF would provide an additional indication for treatment in many of these patients. A recent study using the Manitoba Bone Density Program database prospective cohort has shown that VFA at the time of bone densitometry substantially improves fracture prevention medication use among those with prevalent VFs [18]. Patients with prevalent VFs have the highest risk for more fractures and benefit the most from pharmacologic treatment to reduce the risk of future vertebral and non-vertebral fractures [19–22]. The cost of osteoporotic fractures, using in-hospitalized VFs as an example, was estimated at $746 million annually in the USA [23] and was projected to reach $25 billion in 2025 [24]. VFA has been endorsed as a screening tool by the International Society for Clinical Densitometry (ISCD) [25] and the National Osteoporosis Foundation (NOF). Both have provided guidelines for when VFA should be performed [25, 26]. However, the cost-effectiveness of VFA has not been confirmed.

The purpose of this study was to model the results of five screening strategies, among postmenopausal women at risk for osteoporotic fractures: (1) no screening, (2) central DXA for BMD measurements only, (3) VFA measure only, (4) central DXA followed by VFA if the femoral neck T-score (FN-T) is ≤ − 1.5, or (5) central DXA followed by VFA if the FN-T is ≤ − 1.0. Various screening initiation ages and rescreening intervals were evaluated in order to identify the cost-effectiveness of these different strategies.

## Methods

For the reference-case analysis, an individual-level state-transition model of osteoporosis screening and treatment for community-dwelling postmenopausal women in the USA was constructed. A healthcare sector perspective and a lifetime time horizon were used. The primary model-projected outcome was quality-adjusted life-years (QALY). For each analysis, the incremental cost-effectiveness ratio (ICER) was estimated, which computes cost per QALY gained by comparing four strategies. Two initiation ages, ages 65 and 70 years, and two rescreening intervals, every 5 years and every 10 years, were estimated in the reference-case analysis. The values of key model parameters used for reference-case analysis are presented in Table 1, and the sources of the data are further explained in details below. Reporting of the study was guided by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Appendix Table 4) [46]. The analysis followed recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine and used Python software [47].

### Model structure

Figure 1 provides a simplified representation of the model used for the reference-case analysis, in which cohorts of US community–dwelling postmenopausal women aged ≥ 65 years, with no known fracture history, are screened with (1) DXA BMD measures alone (DXA only); (2) VFA measure alone (VFA only); screened with (3) DXA BMD, followed by the VFA if the femoral neck T-score (FN-T) is ≤ − 1.5 (VFA in FN-T ≤ − 1.5); screened with (4) DXA BMD, followed by the VFA if the FN-T is ≤ − 1.0 (VFA in FN-T ≤ − 1.0); or (5) no screening. Based on a cohort study that consisted of elderly Medicare beneficiaries, we assumed that 25% of the women with osteoporotic FN-T would initiate treatment [12]. We also assumed that 32.3% of the women with the presence of VFs on VFA will lead to pharmacologic intervention regardless of FN-T scores, adopting from a prior US claims

**Table 1** Key model parameters for reference-case analysis

| Parameter | Reference-case value | Source (reference) |
|---|---|---|
| Screening test performance characteristics | | |
| BMD testing sensitivity in women | 0.73 | Sweeney AT et al. [27] |
| BMD testing specificity in women | 1 | Sweeney AT et al. [27] |
| VFA sensitivity[a] | 0.85 | Diogo SD et al. [28] |
| VFA specificity[b] | 0.92 | Diogo SD et al. [28] |
| Demographics | | |
| Prevalence of low bone mass | 60–69 years: 0.534<br>70–79 years: 0.518<br>≥ 80 years: 0.527 | Wright NC et al. [29] |
| Prevalence of osteoporosis | 60–69 years: 0.123<br>70–79 years: 0.257<br>≥ 80 years: 0.349 | Wright NC et al. [29] |
| Prevalence of VF | 60–69 years: 0.046<br>70–79 years: 0.106<br>≥ 80 years: 0.163 | Cosman F. et al. [1] |
| Prevalence of VFA-detected VF relative to BMD[c] | Normal: 0.085<br>Osteopenia: 0.157<br>Osteoporosis: 0.343 | Maghraoui A. et al. [17] |
| All-cause mortality, female, rates per 100,000 population | 65–69 years: 1155.1<br>70–74 years: 1855.8<br>75–79 years: 3028.8<br>80–84 years: 5227.4<br>≥ 85 years: 13080.8 | National Vital Statistics reports [30] |
| Hip fracture–related mortality, first year | 60 years: 0.027<br>80 years: 0.085 | Johnell O et al. [31] |
| VF-related mortality, first year | 60 years: 0.034<br>80 years: 0.085 | Johnell O et al. [31] |
| Wrist fracture–related mortality, first year | 60 years: 0.005<br>80 years: 0.031 | Johnell O et al. [31] |
| Costs, 2017 $US* | | |
| Direct medical costs, annual | | |
| Alendronate[d] | 303 | Red Book [32] |
| Initial hip fracture, Medicare | 18,541 | Song X et al. [33] |
| Initial clinical VF, Medicare | 20,190 | Song X et al. [33] |
| Initial wrist fracture, Medicare | 3486 | Ohsfeldt RL et al. [34] |
| Second fracture (prior hip fracture), Medicare | 42,991 | Song X et al. [33] |
| Second fracture (prior VF), Medicare | 44,526 | Song X et al. [33] |
| Second fracture (prior NHNV[€]), Medicare | 41,987 | Song X et al. [33] |
| Central DXA | 119.6 | Centers for Medicare & Medicaid Services [35] |
| VFA | 69.7 | Centers for Medicare & Medicaid Services [35] |
| Physician visit | 90.6 | Centers for Medicare & Medicaid Services [35] |
| Health state utility values | | |
| No fracture, age 60–69 years | 0.811 | Hanmer J et al. [36] |
| No fracture, age 70–79 years | 0.771 | Hanmer J et al. [36] |
| No fracture, age ≥ 80 years | 0.724 | Hanmer J et al. [36] |
| Hip fracture, age 60–69 years | 0.520 | Derived from utility decrement |
| Hip fracture, age 70–79 years | 0.480 | Brazier JE et al. [37] |
| Hip fracture, age ≥ 80 years | 0.433 | Derived from utility decrement |
| VF, age 60–69 years | 0.740 | Brazier JE et al. [37] |
| VF, age 70–79 years | 0.700 | Derived from utility decrement |
| VF, age ≥ 80 years | 0.653 | Derived from utility decrement |
| Wrist fracture, age 60–69 years | 0.811 | Assumption[e] |

**Table 1** (continued)

| Parameter | Reference-case value | Source (reference) |
|---|---|---|
| Wrist fracture, age 70–79 years | 0.771 | Assumption |
| Wrist fracture, age ≥ 80 years | 0.724 | Assumption |
| Relative risk for fractures[α] in different scenario | | |
| Not on treatment, usual care | | |
| Hip fracture (no prior fracture) | 0.88 | Jackson RD et al. [38] |
| VF (no prior fracture) | 0.90 | Jackson RD et al. [38] |
| Wrist fracture (no prior fracture) | 1.01 | Jackson RD et al. [38] |
| Hip fracture (with prior hip fracture) | 1.80 | Mentol LJ et al. [39] |
| Vertebral fracture (with prior hip fracture) | 2.53 | Gunnes M et al. [40] |
| Wrist fracture (with prior hip fracture) | NA | |
| Hip fracture (with prior VF) | 2.79 | Black DM et al. [41] |
| VF (with prior VF) | 4.10 | Lindsay R et al. [7] |
| Wrist fracture (with prior VF) | 1.49 | Black DM et al. [41] |
| Hip fracture (with prior wrist fracture) | 1.60 | Cuddihy MT et al. [42] |
| VF (with prior wrist fracture) | 5.20 | Cuddihy MT et al. [42] |
| Wrist fracture (with prior wrist fracture) | 2.79 | Cuddihy MT et al. [42] |
| Hip fracture (with LBM) | 0.44 | Cummings SR et al. [43] |
| VF (with LBM) | 0.56 | Cummings SR et al. [43] |
| Wrist fracture (with LBM) | 0.88 | Cummings SR et al. [43] |
| Hip fracture (LBM, prior VF) | 0.49 | Black DM et al. [44] |
| VF (LBM, prior VF) | 0.53 | Black DM et al. [44] |
| Wrist fracture (LBM, prior VF) | 0.52 | Black DM et al. [44] |
| With alendronate treatment | | |
| Hip fracture (LBM, no prior VF) | 0.44 | Cummings SR et al. [43] |
| VF (LBM, no prior VF) | 0.56 | Cummings SR et al. [43] |
| Wrist fracture (LBM, no prior VF) | 0.88 | Cummings SR et al. [43] |
| Hip fracture (with prior VF) | 0.49 | Black DM et al. [44] |
| VF (with prior VF) | 0.53 | Black DM et al. [44] |
| Wrist fracture (with prior VF) | 0.52 | Black DM et al. [44] |

*Costs not presented in 2017 $US inflated to 2017 $US using the Consumer Price Index for Medical Care

[€] *NHNV* non-hip and non-vertebral fractures

[α] Relative risks were used to derived transition probabilities under different scenario

[a, b] The sensitivity and specificity of VFA were both set at 1.00 in the one-way sensitivity analysis [45]

[c] 50% higher and lower of VF incidence were assessed in one-way sensitivity analysis

[d] 25% higher medication costs were assessed in one-way sensitivity analysis

[e] Assumed that the impact of wrist fracture on utility is minimal, which adopted the utility from individuals without fracture

analysis among community-dwelling postmenopausal women [48], and that women identified for treatment would be offered 5 years of alendronate therapy.

The health states a woman may then experience include the following: remaining fracture-free; sustaining a VF, wrist fracture, or hip fracture; experiencing another fragility fracture; and may remain in the community and death. Each woman is able to transit to a different state once every 6 months (cycle length), with the exception of death, which is an absorbing state. Loss of quality of life due to fractures was assigned to the VF states as were the costs associated with fractures. Subsequent fractures increased the costs, loss of quality of life, and probability of mortality, compared with first fracture.

## Test performance and prevalence

The distribution of age-specific FN BMD values was based on updated data from the third NHANES data, from which initial

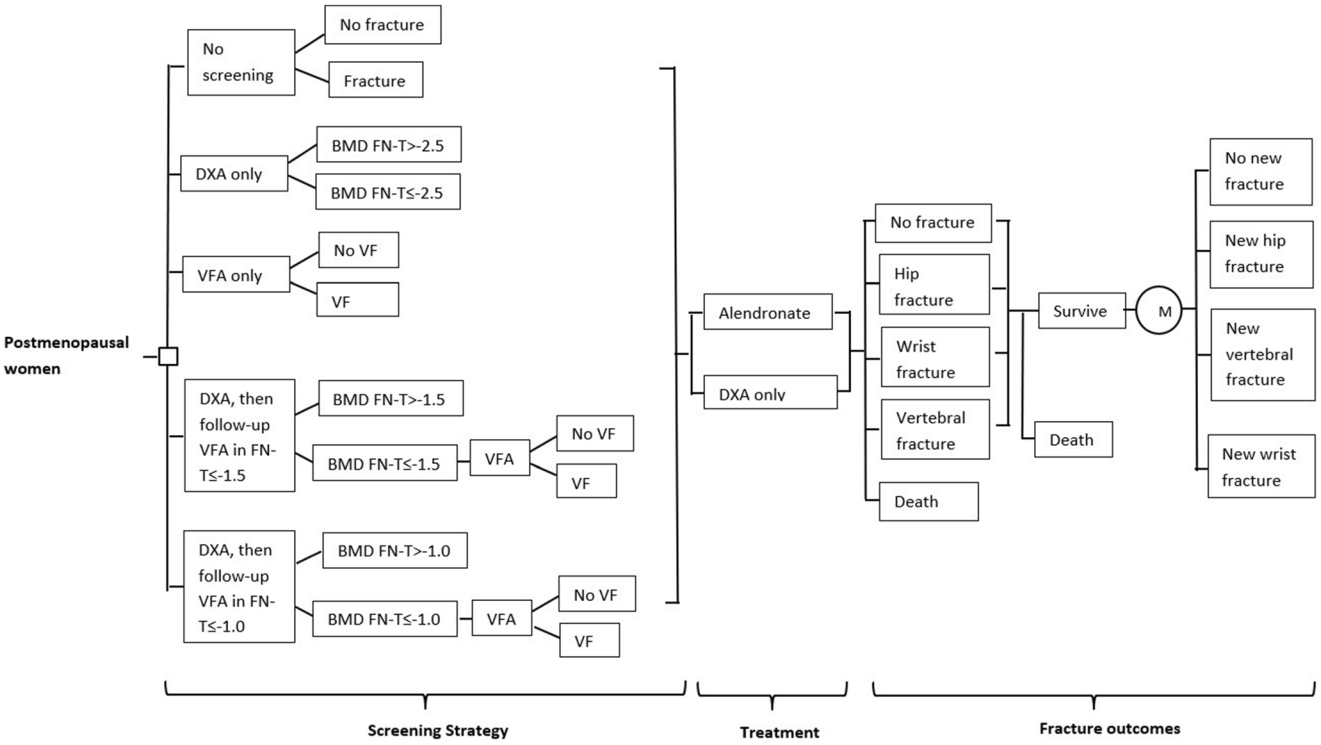



**Fig. 1** Model schematic. This is a simplified representation of the full model used in the reference-case analysis. Four interventional strategies were evaluated as a strategy that was repeated every 5 years and as a strategy repeated every 10 years. No screening was also considered. We assumed that at the time of initial screening, women are in the "no fracture" state, with no prior history of osteoporotic fractures. For the results of the screenings when 32.2% of the women with VFA-detected vertebral fracture or 25% of the women with osteoporosis, a 5-year treatment of alendronate will be offered. Whether patients are on or off treatment, they may experience a series of events over time, including a new osteoporotic fracture, death, or recovery. Women transition from different states on a 6-month cycle (DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; FN-T, femoral neck T-score; VFA, vertebral fracture assessment; VF, vertebral fracture)

FN BMD values were sampled for each simulated woman [49]. The sensitivity and specificity of VFA were 85.1% and 92.4%, respectively, for all grades of VFs on an individual level, according to the results from a population-based study in community-dwelling women aged ≥ 65 years [28]. The prevalence of age-specific asymptomatic VFs in postmenopausal women noted on VFA and its association with BMD values were estimated from the NHANES 2013–2014 data [1]. Those estimates were then adjusted according to BMD values and age, assuming an odds ratio of 1.5 for prevalent VFs for each standard deviation decrease in FN BMD [50, 51], in order to accommodate different combinations of age and BMD thresholds for screening.

## Probabilities of osteoporotic fractures

For community-dwelling postmenopausal women with usual care (calcium and vitamin D), the risk of hip, clinical vertebral, and wrist fractures was obtained from the Women's Health Initiative (WHI) clinical trial [38]. For women with a prior VF, but not receiving alendronate, the risk of subsequent osteoporotic fractures was derived from the Study of Osteoporotic Fractures cohort as well as pooled data of 4 large 3-year osteoporosis treatment RCTs that consisted of women who have been randomly assigned to a placebo group [7, 41]. For women not receiving alendronate but with low bone mass (LBM) or with both LBM and prior VFs, the risk of different types of fractures was estimated from the Fracture Intervention Trial [43, 44]. The risk of subsequent fractures in treatment-naive women with prior hip fractures or wrist fractures was estimated from a series of large retrospective studies of fracture recurrence in Rochester, MN [39, 42], as well as a population-based survey [40]. For women receiving alendronate, the risk of osteoporotic fractures in women without prior VFs was calculated based on data from the Fracture Intervention Trial (clinical fracture arm), the Alendronate Phase III Osteoporosis Treatment Study Groups, and a meta-analysis of 5 completed RCTs on alendronate [19, 43, 52, 53]. The risk of subsequent fractures in alendronate-treated women with prior VFs was estimated from the Fracture Intervention Trial (vertebral fracture arm) [44].

## Treatment

Treatment of generic alendronate at a dosage of 70 mg once weekly was initiated in the following conditions: (1) 25% of the women with BMD values in the osteoporosis range; (2) 32.3% of the women presence of mild, moderate, and severe

VFs identified on VFA; and (3) women who experienced a clinical osteoporotic fracture including VF, wrist fracture, or hip fracture [54]. The adherence was assumed at 100% for the reference-case analysis. A 5-year period of alendronate treatment was modeled, followed by a drug holiday for 5 years (consistent with current recommendations about long-term bisphosphonate use) [55, 56]. This 5-year treatment pattern was used for the rest of a woman's lifetime. The benefits of alendronate after 5 years of treatment linearly decline during the 5-year drug holiday period, which was modeled as a function of age and hip BMD at discontinuation [57].

### Mortality

Age-specific background mortality in women aged 65 years or above was extracted from US National Vital Statistics [58]. Excess mortality within 5 years following different types of osteoporotic fractures was estimated from a Swedish cohort that consisted of 2847 patients with a fragility fracture [31].

### Costs

From a healthcare sector perspective, we included direct medical costs of alendronate treatment, physician visits, screening tests, and fracture-related treatment. The annual cost of alendronate was estimated according to the average US wholesale price for 2017 [32]. Direct medical costs due to first fracture as well as subsequent fractures were estimated from the 2008 MarketScan Medicare database, which includes individuals who have both Medicare coverage and supplemental employer-sponsored coverage [33]. The database includes Medicare-covered portion of payment, the employer-paid portion, and any patient out-of-pocket expenses. Costs for one annual level 3 follow-up physician visit while on alendronate, screening tests of BMD DXA, and VFA were obtained from 2017 national-average Medicare reimbursement rates [35]. All costs are reported in 2017 US dollars; the Consumer Price Index for Medical Care was used when necessary. A 3% annual discount rate was applied to costs [47, 59].

### Quality-adjusted life-years

The baseline QALY of community-dwelling postmenopausal women aged ≥ 65 years without fractures were obtained from a report of nationally representative non-institutionalized US adult population [36]. Decreased QALY for the first 6 months and subsequent years after incident hip, clinical vertebral, and wrist fractures were estimated from a systematic review of osteoporosis-related conditions [37]. Derived fracture- and age-specific utilities were estimated from utility decrement. A 3% annual discount in QALY rate was applied [47].

### Analyses

Both the reference-case analysis and scenario sensitivity analysis were performed for both screening initiation ages and rescreening frequencies. In order to determine the optimal screening strategy, we first excluded all dominated screening strategies, that is, strategies that were more costly and less effective than alternatives or their combinations. For all remaining strategies, the ICERs were calculated. Optimal strategy was then determined applying a threshold for the willingness-to-pay (WTP) per QALY gained of $100,000.

Scenario analysis evaluating the impact of key model parameters was conducted, including VF risk (50% higher and 50% lower), costs of fracture treatment (25% higher), effectiveness of alendronate (25% lower), and improved sensitivity and specificity of VFA (upper limits of test performance from meta-analysis [45]).

## Results

### Reference-case analysis

In the reference-case analysis, regardless of initiation age and rescreening intervals, the three strategies including VFA dominated DXA only and no screening (Table 2). VFA in FN-T ≤ − 1.0 at age 65 years with rescreening every 5 years increased life expectancy from 84.6 years with no screening to 84.7 years. It also reduced the number of subsequent osteoporotic fractures by approximately 3.7% and 7.7%, compared with DXA only and no screening, respectively. Particularly, VFA in FN-T ≤ − 1.0 reduced the number of clinical VFs by 3.2% and 8.5%, respectively, relative to DXA only and no screening. Moreover, the incorporation of VFA significantly enhanced the initiation of pharmacologic intervention by 7.3% and 42.7%, respectively, than that of using DXA only and no screening.

The cost-effectiveness of screening strategies varied, but regardless of initiation ages and rescreening intervals, VFA in FN-T ≤ − 1.0 was the most cost-effective strategy. Assuming a willingness-to-pay of $100,000 per QALY, starting screening at age 65 years old with a rescreening frequency of every 5 years, VFA in FN-T ≤ − 1.0 was cost-effective with an ICER of $40,792 per QALY (Table 2). The incremental cost per QALY gained for this strategy increased slightly as the rescreening interval increased to every 10 years, yielding an ICER of $41,818 per QALY. If the initiation age was 70 years old with a rescreening interval of every 5 years, VFA in FN-T ≤ − 1.0 remained cost-effective with an ICER of $14,371 per QALY. When a rescreening frequency of every 10 years was evaluated, the incremental cost per QALY gained for VFA in FN-T ≤ − 1.0 decreased, yielding an ICER of $4717 per QALY.

**Table 2** Reference-case analysis for five strategies, from a healthcare perspective

| Strategies | Lifetime costs ($)* | Quality-adjusted life-years (QALY) | Incremental cost-effectiveness ratio (ICER) |
|---|---|---|---|
| Starting at age 65 years, test freq every 5 years | | | |
| No screening | 25,776 | 14.9994 | Dominated by DXA only |
| DXA only | 25,600 | 15.0247 | Dominated by VFA only |
| VFA only | 24,689 | 15.0383 | Ref |
| DXA FNT $\leq -1.5$ + VFA | 25,145 | 15.0436 | Dominated by DXA FNT $\leq -1.0$ + VFA |
| DXA FNT $\leq -1.0$ + VFA | 25,101 | 15.0484 | 40,792 (relative to VFA only) |
| Starting at age 65 years, test freq every 10 years | | | |
| No screening | 25,748 | 15.0009 | Dominated by DXA only |
| DXA only | 25,675 | 15.0126 | Dominated by VFA only |
| VFA only | 25,062 | 15.0230 | Ref |
| DXA FNT $\leq -1.5$ + VFA | 25,331 | 15.0261 | Dominated by DXA FNT $\leq -1.0$ + VFA |
| DXA FNT $\leq -1.0$ + VFA | 25,292 | 15.0285 | 41,818 (relative to VFA only) |
| Starting at age 70 years, test freq every 5 years | | | |
| No screening | 24,053 | 11.8100 | Dominated by DXA only |
| DXA only | 23,583 | 11.8427 | Dominated by VFA only |
| VFA only | 22,971 | 11.8450 | Ref |
| DXA FNT $\leq -1.5$ + VFA | 23,257 | 11.8572 | Dominated by DXA FNT $\leq -1.0$ + VFA |
| DXA FNT $\leq -1.0$ + VFA | 23,188 | 11.8601 | 14,371 (relative to VFA only) |
| Starting at age 70 years, test freq every 10 years | | | |
| No screening | 24,082 | 11.8108 | Dominated by DXA only |
| DXA only | 23,599 | 11.8341 | Dominated by VFA only |
| VFA only | 23,208 | 11.8347 | Ref |
| DXA FNT $\leq -1.5$ + VFA | 23,318 | 11.8427 | Dominated by DXA FNT $\leq -1.0$ + VFA |
| DXA FNT $\leq -1.0$ + VFA | 23,258 | 11.8453 | 4717 (relative to VFA only) |

*Costs were expressed in 2017 $US

To identify the most cost-effective strategy across screening intervals, ICER was calculated for each strategy compared with the next less effective non-dominated strategy (data not shown). Assuming a willingness-to-pay of $100,000 per QALY and initiating screening at age 65 years, VFA in FN-T $\leq -1.0$ with rescreening interval every 5 years was the best strategy ($40,792 per QALY). If starting at age 70 years, VFA in FN-T $\leq -1.0$ with rescreening interval every 5 years was still the best strategy ($14,371 per QALY).

## Scenario analyses

VFA-based strategies remained cost-effective despite variations in several key parameter assumptions (Table 3). Assuming the VF incidence increased by 50% and a willingness-to-pay of $100,000 per QALY, VFA in FN-T $\leq -1.0$ initiated at age 65 years with rescreening every 5 years resulted in an ICER of $84,082 per QALY, but this strategy was no longer cost-effective with an initiation age of 65 years and a rescreening interval every 10 years. The incremental cost per QALY gained decreased to $24,167 if VFA in FN-T $\leq -1.0$ starting at age 70 years old with a rescreening interval of 5 years. This strategy was even more cost-effective ($4884 per QALY gained) if a rescreening interval increased to 10 years. If VF incidence was assumed to decrease by 50%, VFA in FN-T $\leq -1.0$ initiated at age 65 years with a rescreening interval of every 5 years was the most cost-effective ($3571 per QALY). However, if increasing the rescreening interval to 10 years, VFA in FN-T $\leq -1.5$ was cost-effective ($17,431 per QALY gained). VFA in FN-T $\leq -1.0$ remained the most cost-effective if starting at age 70 years, regardless of rescreening interval. When we evaluated the impact of advances in test performance of VFA, according to a

**Table 3** Scenario analysis for five strategies, from a healthcare perspective

| Strategies | Lifetime costs ($)* | Quality-adjusted life-years |
|---|---|---|
| If VF incidence increase by 50% | | |
| Starting at age 65 years, test freq every 5 years | | |
| No screening | 32,002 | 14.8804 |
| DXA only | 31,546 | 14.9067 |
| VFA only | 30,147 | 14.9386 |
| DXA FNT ≤ − 1.5 + VFA | 30,703 | 14.9384 |
| DXA FNT ≤ − 1.0 + VFA | 30,559 | 14.9435 |
| Starting at age 65 years, test freq every 10 years | | |
| No screening | 31,992 | 14.8832 |
| DXA only | 31,751 | 13.8982 |
| VFA only | 30,815 | 14.9185 |
| DXA FNT ≤ − 1.5 + VFA | 31,203 | 14.9171 |
| DXA FNT ≤ − 1.0 + VFA | 31,119 | 14.9187 |
| Starting at age 70 years, test freq every 5 years | | |
| No screening | 29,916 | 11.7071 |
| DXA only | 29,056 | 11.7442 |
| VFA only | 28,078 | 11.7564 |
| DXA FNT ≤ − 1.5 + VFA | 28,389 | 11.7662 |
| DXA FNT ≤ −1.0 + VFA | 28,339 | 11.7672 |
| Starting at age 70 years, test freq every 10 years | | |
| No screening | 29,972 | 11.7064 |
| DXA only | 29,186 | 11.7318 |
| VFA only | 28,528 | 11.7408 |
| DXA FNT ≤ − 1.5 + VFA | 28,649 | 11.7474 |
| DXA FNT ≤ − 1.0 + VFA | 28,570 | 11.7494 |
| If VF incidence decrease by 50% | | |
| Starting at age 65 years, test freq every 5 years | | |
| No screening | 19,558 | 15.1161 |
| DXA only | 19,686 | 15.1378 |
| VFA only | 19,183 | 15.1385 |
| DXA FNT ≤ − 1.5 + VFA | 19,584 | 15.1497 |
| DXA FNT ≤ − 1.0 + VFA | 19,589 | 15.1511 |
| Starting at age 65 years, test freq every 10 years | | |
| No screening | 19,514 | 15.1156 |
| DXA only | 19,602 | 15.1267 |
| VFA only | 19,304 | 15.1287 |
| DXA FNT ≤ − 1.5 + VFA | 19,494 | 15.1369 |
| DXA FNT ≤ − 1.0 + VFA | 19,522 | 15.1358 |
| Starting at age 70 years, test freq every 5 years | | |
| No screening | 18,202 | 11.9142 |
| DXA only | 18,138 | 11.9399 |
| VFA only | 17,781 | 11.9346 |
| DXA FNT ≤ − 1.5 + VFA | 18,082 | 11.9492 |
| DXA FNT ≤ − 1.0 + VFA | 18,100 | 11.9496 |
| Starting at age 70 years, test freq every 10 years | | |
| No screening | 18,196 | 11.9137 |
| DXA only | 18,022 | 11.9323 |
| VFA only | 17,845 | 11.9285 |
| DXA FNT ≤ − 1.5 + VFA | 17,955 | 11.9398 |
| DXA FNT ≤ − 1.0 + VFA | 17,945 | 11.9400 |
| If sensitivity and specificity of VFA increase to 1 | | |
| Starting at age 65 years, test freq every 5 years | | |
| No screening | 25,765 | 14.9998 |
| DXA only | 25,602 | 15.0230 |
| VFA only | 24,422 | 15.0403 |
| DXA FNT ≤ − 1.5 + VFA | 25,018 | 15.0441 |
| DXA FNT ≤ − 1.0 + VFA | 24,943 | 15.0474 |
| Starting at age 65 years, test freq every 10 years | | |
| No screening | 25,737 | 14.9976 |
| DXA only | 25,664 | 15.0114 |
| VFA only | 24,838 | 15.0265 |
| DXA FNT ≤ − 1.5 + VFA | 25,224 | 15.0265 |
| DXA FNT ≤ − 1.0 + VFA | 25,175 | 15.0287 |
| Starting at age 70 years, test freq every 5 years | | |
| No screening | 24,056 | 11.8097 |
| DXA only | 23,592 | 11.8441 |

**Table 3** (continued)

| Strategies | Lifetime costs ($)* | Quality-adjusted life-years |
|---|---|---|
| VFA only | 22,725 | 11.8472 |
| DXA FNT ≤ − 1.5 + VFA | 23,144 | 11.8597 |
| DXA FNT ≤ − 1.0 + VFA | 23,081 | 11.8594 |
| Starting at age 70 years, test freq every 10 years | | |
| No screening | 24,045 | 11.8108 |
| DXA only | 23,606 | 11.8324 |
| VFA only | 22,978 | 11.8355 |
| DXA FNT ≤ − 1.5 + VFA | 23,222 | 11.8447 |
| DXA FNT ≤ − 1.0 + VFA | 23,170 | 11.8450 |
| If osteoporosis-related medication cost increased by 25% | | |
| Starting at age 65 years, test freq every 5 years | | |
| No screening | 26,093 | 14.9993 |
| DXA only | 26,091 | 15.0235 |
| VFA only | 25,179 | 15.0390 |
| DXA FNT ≤ − 1.5 + VFA | 25,655 | 15.0444 |
| DXA FNT ≤ − 1.0 + VFA | 25,645 | 15.0481 |
| Starting at age 65 years, test freq every 10 years | | |
| No screening | 26,071 | 14.9987 |
| DXA only | 26,064 | 15.0121 |
| VFA only | 25,454 | 15.0263 |
| DXA FNT ≤ − 1.5 + VFA | 25,745 | 15.0265 |
| DXA FNT ≤ − 1.0 + VFA | 25,741 | 15.0267 |
| Starting at age 70 years, test freq every 5 years | | |
| No screening | 24,336 | 11.8105 |
| DXA only | 24,084 | 11.8435 |
| VFA only | 23,376 | 11.8447 |
| DXA FNT ≤ − 1.5 + VFA | 23,770 | 11.8582 |
| DXA FNT ≤ − 1.0 + VFA | 23,744 | 11.8613 |
| Starting at age 70 years, test freq every 10 years | | |
| No screening | 24,338 | 11.8101 |
| DXA only | 24,035 | 11.8321 |
| VFA only | 23,585 | 11.8350 |
| DXA FNT ≤ − 1.5 + VFA | 23,733 | 11.8435 |
| DXA FNT ≤ − 1.0 + VFA | 23,706 | 11.8457 |

*Costs were expressed in 2017 $US

systematic review and meta-analysis, the sensitivity and specificity of VFA were up to 1.00 in some published studies [45]. If this is the case, VFA in FN-T ≤ − 1.0 initiated at age 65 years with a rescreening interval of every 5 years was cost-effective with an ICER of $73,380 per QALY. This strategy remained cost-effective if starting at age 70 years, assuming a willing-to-pay of $100,000 per QALY. Lastly, if the medication costs were increased by 25%, VFA in FN-T ≤ − 1.0 was still the most cost-effective strategy with an ICER of less than $50,000 per QALY, except for an initiation age of 65 years and a rescreening interval of 10 years.

## Discussion

The reference-case analysis has demonstrated that the identification of prevalent VFs through a VFA at the same time as having a routine DXA BMD test results is cost-effective in community-dwelling postmenopausal women, due to reductions in subsequent osteoporotic fracture incidence and costs to treat these fractures. VFA could save approximately 30 billion dollars given that there are 28.3 million postmenopausal women age 65 and older in the USA [60]. Moreover, VFA resulted in a slight improvement in quality-adjusted life-years, since the risk of mortality with time after fractures decreases and medications have limited impact on mortality [61]. Overall, central DXA followed by VFA if the FN-T ≤ − 1.0 was most cost-effective. Because of the large economic burden of osteoporotic fractures in the USA, the need to reduce costs associated with their treatment should be a health policy priority.

It is known that the majority of osteoporotic fractures occur in people with BMD values that are not in the osteoporosis range [62–64]. According to the Rotterdam study, only 44% of all non-vertebral fractures occurred in women with an osteoporotic BMD [64]. The risk of fracture is multi-factorial, and many independent risk factors contribute to risk over and above that reflected by BMD [65]. Among those, prevalent VF is a significant independent risk factor of future osteoporotic fractures [66, 67]. Hence, if women are selected for pharmacologic intervention on the basis of osteoporotic BMD values alone, a large proportion of patients will miss the opportunity to be treated. The data from DXA-alone strategy in our study supported that using thresholds of FN-T ≤ − 2.5 for treatment is insufficient to reduce the number of women who sustain osteoporotic fractures

over time. Currently, the NOF guidelines recommend pharmacological intervention in women (1) with hip fracture or VFs; (2) with BMD FN-T scores ≤ − 2.5; or (3) postmenopausal women with low BMD and a 10-year hip fracture probability ≥ 3% or a 10-year major osteoporotic fracture probability ≥ 20% using the Fracture Risk Assessment Tool (FRAX®) [26, 68]. Our results suggest a need to promote targeted treatment protocols for women with low BMD and VFs due to their increased risk for subsequent fractures.

One of the major findings of the current study is that VFA is beneficial even in women who have osteoporotic BMD values, which, to our knowledge, has not been assessed in previous studies. For example, Schousboe et al. evaluated the cost-effectiveness of VFA in postmenopausal women with a FN-T > − 2.5 and concluded that VFA is cost-effective for women aged 60 to 80 years with a FN-T of − 2.0 to − 2.4 [69]. However, it is worth noting that less than one-fourth of the women with osteoporosis actually initiate the treatment and even fewer adhere to the medications after 1 year [70–72]. Identification of VFs may alter the decision to initiate pharmacotherapy [18]. A study has shown that knowledge of VFs may influence patients' perceived need for fracture prevention medication and therefore medication compliance [73].

The fact that VFA enhances the treatment of osteoporosis is of particular importance in preventing fractures. Although the benefits of bisphosphonates have been observed in RCTs [74], it is difficult to obtain the same treatment effects outside clinical trial settings due to non-adherence and low treatment rate. The reasons for low initiation rate or discontinuation of bisphosphonates are not well understood, but proposed factors include fear of adverse events, actual occurrence of adverse events, requirement for more physician visits, higher out-of-pocket drug payments, and higher comorbidities [75]. In addition, physicians are less likely to prescribe medications with increasing patient age [72], which may be explained by their belief of the irreversible natural history of osteoporosis in the elderly. In contrast, substantial reductions in osteoporotic fractures can be accomplished by aggressively treating women with low bone mass and VFs.

We know that the incidence of osteoporotic fractures dramatically increases as women get older [1, 2]. This is also true for subsequent fractures following prevalent or incident VFs [76]. Given that even small improvements in bone density by treatment can substantially reduce fracture risk [77], the implementation of VFA can favorably affect treatment efficacy by altering adherence behaviors and increasing physicians' awareness of treatment.

Notably, in our model, we have incorporated the costs associated with second fractures following an initial osteoporotic fracture, which has not been clearly distinguished in similar analyses [69, 78, 79]. According to a systematic review of healthcare costs and resource utilization related to osteoporotic fractures in the USA, the medical costs in the year following a fracture were 1.6–6.2 times higher than pre-fracture costs [80]. Moreover, total healthcare costs were the highest in women aged ≥ 65 years, and hip fractures were the most expensive [80]. Song and colleagues found that patients with second fractures had medical costs that were 2–3 times higher on average compared with those who had single fractures, using medical claims database [33]. Thus, without accounting for the dramatic increase in medical costs as well as indirect costs, the costs of fracture-related treatment might be largely underestimated.

The combined strategy of DXA scan along with VFA can be easily implemented from a practical perspective. The NOF guidelines recommend DXA scans in community-dwelling women age 65 and older for osteoporosis, which aligns with our simulated cohort for VFA. Although VFA is still inferior to X-rays in visualizing vertebrae properly in the upper thoracic spine (i.e., Th5 to Th8 levels) due to the overlay of tissues, VFA still performs well in recognizing moderate or severe VFs [81, 82]. It is arguable that mild VFs may be of less clinical importance than those moderate or severe ones. Moreover, advances in imaging technology will further improve the performance of VFA over time, and therefore, VFA-based strategies would be expected to be more effective. However, future economic analysis may be needed to see if the same conclusions hold while taking the geographic availability of DXA into consideration [83].

Our study has several limitations. First of all, we only included hip, clinical vertebral, and wrist fractures which are the most commonly observed osteoporotic fractures and therefore allow us to obtain more accurate data from published studies compared with less recognized osteoporotic fractures. However, other fractures are of less impact on subsequent fractures, and if treatment is effective in reducing the risk of other fractures, the screening strategies evaluated may result in cost-saving. Second, the medication adherence to alendronate was assumed at 100%, which is overestimated. However, in a cost-effectiveness analysis of different screening strategies for osteoporosis in postmenopausal women, the author assumed a medication adherence rate of 50% while 100% treatment for osteoporosis; the results indicated that treatment was still cost-effective [79]. In our model, only 25% of the women with osteoporosis initiated the treatment that may offset an overestimation in compliance. Moreover, when the treatment effectiveness was lowered by 25%, the sensitivity analysis showed that our results were robust. Third, adverse events due to long-term alendronate treatment were not included in the model as few events were seen either in trials or observational studies [84]. Also, in the present analysis, anabolic treatments, clearly more expensive, were not considered, as a previous cost-effectiveness analysis has shown that therapy with teriparatide alone is more expensive and produces a smaller increase in QALY than alendronate [54]. Fourth, most clinical trials assessing the effectiveness of antiresorptive agents focused on women with BMD T-score ≤ − 2.0 or on women with prevalent VFs [43, 44]. Little data exist to show that available therapeutic regiments are also effective at reducing the risk of future fractures

in women with BMD T-scores between −2.0 and −1.0 or in women with prior fractures other than VFs. Therefore, we had to calculate reduced fracture risk in these women due to treatment, given that preservation of bone quality would be expected to protect against fractures over time [85, 86]. Future economic analysis may be warranted when real-world data become available to see if the same conclusion holds. Fifth, in practice, physicians also use FRAX scores, which was not considered in the present analysis, to treat those at high fracture risk. Future studies that incorporate FRAX in combination with DXA or VFA may also be considered. Lastly, the risk of subsequent fractures appears to depend on the number and severity of existing VFs, but we only considered the presence of VF in the model [87, 88]. It is possible that the VFA-based strategy will be more cost-effective in women with mild VFs while less cost-effective in women with severe or multiple VFs, which has been partially suggested in our sensitivity analysis.

## Conclusion

Our results support the NOF guidelines regarding the use of vertebral imaging. We also provide evidence in alignment with the ISCD positions on VFA which indicated that the diagnostic use of VFA may serve as a potential alternative to conventional X-rays to identify prevalent VFs in the screening of people at risk for osteoporotic fractures [25]. This is the first economic analysis that showed that VFA-based strategy is cost-effective in community-dwelling postmenopausal women as a screening tool for increased risk of osteoporotic fractures. The combined strategy of DXA and VFA should be implemented and expanded in the routine care in order to reduce the burden of osteoporotic fractures.

**Availability of data and material** Publically

## Compliance with ethical standards

**Conflicts of interest** Jingyan Yang was a student of Columbia University at the time this work was conducted and is currently employed by Pfizer Inc. Jeri W. Nieves receives study drug from Eli Lilly and Radius Health. Felicia Cosman consults for, serves as advisor for, and receives lecture fees from Amgen and Radius. She previously received consulting, advising, and speaking fees from Eli Lilly and advisory fees from Merck. She also received grant support from Eli Lilly and Amgen. Patricia W. Stone has no conflicts. Meng Li has no conflicts.

**Ethics approval** Not applicable

**Consent to participate** Not applicable

**Consent for publication** Yes

**Code availability** Not applicable

## Appendix

**Table 4** Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist

| Section/item | Item no. | Recommendation | Reported page no. |
|---|---|---|---|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation and describe the interventions compared. | 1 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods, results, and conclusions. | 2 |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | 2, 5 |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroup analyzed, including why they were chosen. | 2, 6 |
| Setting and location | 5 | State relevant aspects of the systems in which the decision(s) need(s) to be made. | 2, 6 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | 2, 6 |
| Comparators | 7 | Describe the interventions or strategies being compared and stated why they were chosen. | 2, 6, Fig. 1 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | 2, 6 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | 8 |
| Choice of health outcomes | 10 | | 2, 6 |

**Table 4** (continued)

| Section/item | Item no. | Recommendation | Reported page no. |
|---|---|---|---|
| | | Describe what outcomes were used as the measure(s) of benefits in the evaluation and their relevance for the type of analysis performed. | |
| Measurement of effectiveness | 11b | Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | 8 |
| Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | N/A |
| Estimating resources and costs | 13b | Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | 8 |
| Currency, price date, a nd conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | 8 |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | 6 |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | 6–8 |
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments to a model; and methods for handling population heterogeneity and uncertainty. | 6–8 |
| Results | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distribution for all parameters. Report reasons or sources for distribution used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | 7–8 and Table 1 |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | 9 and Table 2 |
| Characterizing uncertainty | 20b | Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | 10 and Table 3 |
| Characterizing heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | 9 |
| Discussion | | | |
| Study findings, limitations, generalizability, and current knowledge | 22 | Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge. | 10–13 |

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