National Institute for Health and Care Excellence

Draft for consultation

Osteoporosis: risk assessment

[G] Diagnosing vertebral fractures with DXA based VFA

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.1-1.5.4 and recommendation for research in the NICE guideline

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Draft for Consultation

This evidence review was developed by NICE

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1. Diagnosing vertebral fractures with DXA based VFA

1.1. Review question: What is the diagnostic accuracy of DXA with vertebral fracture assessment (VFA) for identifying vertebral fractures?

1.1.1. Introduction

Vertebral fractures are the most common form of 'fragility' fracture associated with osteoporosis and have traditionally been diagnosed using conventional radiography (X-rays), which produces ionising radiation. This review question examines whether vertebral fracture assessment (VFA) conducted using dual-energy X-ray absorptiometry (DXA) densitometric scanners can be used to identify vertebral fractures.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years and older) who are having a dual-energy X-ray absorptiometry (DXA) assessment.
Target condition	Vertebral fracture
Index test	DXA with vertebral fracture assessment (VFA)
Reference standard	Expert radiological assessment of X-ray, MRI, or CT
Statistical measures	All outcomes are considered equally important for decision making and therefore have all been rated as critical. Accuracy of estimation of vertebral fracture: • Sensitivity/ specificity • Positive and negative likelihood ratio • Positive and negative predictive value • Area under the curve (AUC)
Study design	Diagnostic: cohort and cross-sectional studies

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Diagnostic evidence

1.1.4.1. Included studies

Twenty-three studies were included in the review and are summarised in Table 2. Twenty-three studies assessed DXA with vertebral fracture assessment (VFA) with radiological assessment of conventional radiography (X-ray) as the reference standard. One study (van

Dort 2018) also assessed DXA with VFA using chest computed tomography (chest CT) as the reference standard. No studies with magnetic resonance imaging (MRI) were identified.

Diagnostic accuracy studies were classified as cross sectional if DXA with VFA and conventional radiography were conducted within 2 weeks of each other, and as cohort studies if the period between the tests was more than this. Sixteen studies were cross sectional (Bazzocchi 2012, Binkley 2005, Chapurlat 2006, Damiano 2006, Deleskog 2016, Diacinti 2012A, Diacinti 2012B, Domiciano 2013, Ferrar 2000, Ferrar 2008, Hospers 2009, Lee 2014, Mazzaoferro 2006, Rea 200B, Rud 2016, Schousboe 2006), 4 were prospective cohort studies (Ferrar 2000, Ferrar 2003, Sullivan 2011, Vokes 2003), and 4 were retrospective cohort studies (Fuerst 2009, Lin 2017, Malgo 2017, van Dort 2018). Two studies (Ferrar 2000, Ferrar 2008) reported data for two separate populations. Ferrar 2000 reported data for an osteoporotic reference population at low risk of vertebral fracture using a prospective cohort design. Ferrar 2008 reported data for women at low risk of osteoporotic fracture and women at high risk of osteoporotic fracture. Evidence from all included studies is summarised in Table 3, Table 4, and Table 5.

Twelve studies were conducted in postmenopausal women, whilst 8 studies were conducted in adults. Four studies were conducted in specific populations at increased risk of fracture due to secondary osteoporosis, including adults participating in a COPD-related osteoporosis trial (van Dort 2018), adults on standard triple or double immunosuppressive therapy (Mazzoferro 2006), men with non-metastatic cancer (Sullivan 2011), and women ≥ 50 years old with rheumatoid arthritis (Lee 2014).

The definition of vertebral fracture (VF) that was most used in the studies was the visual semi-quantitative (VSQ) method of Genant, with the remaining studies using either visual interpretation only, a composite sequential method (for example, VSQ then QM), or different definitions at the reference and index test level. Identification of VF by category of fracture severity (mild, moderate, or severe) was determined by percentage decrease in vertebral height (≥20% to 25%, 25% to 40%, >40% respectively) as detected by the relevant method used to define VF. Most studies reported the diagnostic accuracy of DXA with VFA to identify Grade 1 or worse fractures (mild, moderate, and severe) and Grade 2 or worse fractures (moderate and severe). Most studies also reported data for both the per-vertebra analysis (PVA) and per-person analysis (PPA), enabling consideration of its ability to identify fractured vertebra and its ability to identify a person with a fractured vertebra. Radiological assessment of conventional radiographs was conducted by a trained expert (for example, radiologist) in all studies.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, sensitivity and specificity forest plots in Appendix E, ROC plots in Appendix F, and QUADAS-2 assessments in Appendix G.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix K.

1.1.5. Summary of studies included in the diagnostic evidence review

Table 2: Summary of studies included in the evidence review

Study Type of study	Population Number of participants (M/F)	Mean age (SD), range	Index test	Reference standard Prevalence of VF[a]	Fracture severity Definition of vertebral fracture	Outcomes
Bazzocchi 2012 Cross-sectional	Adults with indication for spinal radiography N=68 (38/30)	58.1 years (9.6)	DXA with VFA	Conventional radiography PVA: 2.2% PPA: 38.2%	Grade 1+, 2+ VSQ-G then QM (MXA) v VSQ-G then QM (MRX)	• Sensitivity/specificity • PPV/NPV • PLR/NLR • AUC
Binkley 2005 Cross-sectional	Postmenopausal women receiving osteoporosis treatment or having BMD assessment N=79	72.8 years (0.5), 61-84	DXA with VFA	Conventional radiography PVA: 4.8%	Grade 1+, 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Chapurlat 2006 Cross-sectional	Postmenopausal women having BMD assessment N=85	71.0 years	DXA with VFA	Conventional radiography PPA: 50.6%	Grade 1+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Damiano 2006 Cross-sectional	Postmenopausal women with indication for spinal radiography N=133	69.1 years (10), 37-96	DXA with VFA	Conventional radiography PVA: 8.8% PPA: 52%	Grade 1+, 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR

Study Type of study	Population Number of participants (M/F)	Mean age (SD), range	Index test	Reference standard Prevalence of VF[a]	Fracture severity Definition of vertebral fracture	Outcomes
Deleskog 2016 Cross-sectional	Adults with severe osteoporosis and receiving osteoporosis treatment N=35 (5/30)	67.5 years	DXA with VFA	Conventional radiography PVA: 38.9%	Grade 1+, 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Diacinti 2012A Cross-sectional	Peri- and post-menopausal women and men referred for osteoporosis; and adults participating in HIV-related osteoporosis study N=350 (81/269)	60.6 years (11.6), 28-85)	DXA with VFA	Conventional radiography PVA: 5.1% PPA: 36.0%	Grade 1+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Diacinti 2012B Cross-sectional	Postmenopausal women referred for osteoporosis evaluation N=930	62.4 years (11.6), 46-85	DXA with VFA	Conventional radiography PVA: 3.7% PPA: 27.0%	Grade 1+ Visual-ABQ then VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Domiciano 2013 Cross-sectional	Adults≥65-years old, N=429	73.0 years (5.1)	DXA with VFA	Conventional radiography PVA: 4.4% PPA: 29.4%	Grade 1+, 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Ferrar 2000	Women with osteoporosis and radiologically	70.0 years (9.0), 49-87;	DXA with VFA	Conventional radiography	Grade 1+	• Sensitivity/specificity • PPV/NPV

Study Type of study	Population Number of participants (M/F)	Mean age (SD), range	Index test	Reference standard Prevalence of VF[a]	Fracture severity Definition of vertebral fracture	Outcomes
Prospective cohort; cross-sectional	confirmed VF (Osteoporotic population), N=83; Women registered with GP (Reference population), N=123	66.6 years (7.3), 56-88		PVA: 33.3%; PVA: 1.7%	Visual-unspecified then VSQ-G Visual-unspecified	• PLR/NLR
Ferrar 2003 Prospective cohort	Women with osteoporosis referred to bone clinic, N=70	67.0 years	DXA with VFA	Conventional radiography PVA: 37.3%	Grade 1+, 2+ Visual-unspecified	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Ferrar 2008 Cross-sectional	Postmenopausal women with osteoporosis and at low risk of osteoporotic-VF, N=459; Postmenopausal women with osteoporosis and at high risk of osteoporotic-VF, N=298	68.0 years (7), 55-79; 69.1 years (7), 55-80	DXA with VFA	Conventional radiography PPA: 11.3%; PPA: 28.9%	Grade 1+, 2+ Visual-ABQ	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Fuerst 2009 Retrospective cohort	Postmenopausal women with osteoporosis, N=203	67.5 years (9.6)	DXA with VFA	Conventional radiography PVA: 4.8%	Grade 1+, 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Hospers 2009	Adults≥50 years-old with suspected	62.0 years, range 25-89	DXA with VFA	Conventional radiography	Grade 1+	• Sensitivity/specificity • PPV/NPV

Study Type of study	Population Number of participants (M/F)	Mean age (SD), range	Index test	Reference standard Prevalence of VF[a]	Fracture severity Definition of vertebral fracture	Outcomes
Cross-sectional	osteoporosis referred for BMD assessment, N=250 (60/190)			PVA: 46.5%	VSQ-Other	• PLR/NLR
Lee 2014 Cross-sectional	Women≥50 years-old with rheumatoid arthritis, N=100	61.2 years (8.2)	DXA with VFA	Conventional radiography PPA: 47%	Grade 1+ QM (MXA or MRX as appropriate) then VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Lin 2017 Retrospective cohort	Postmenopausal women referred for osteoporosis evaluation, N=114	NR	DXA with VFA	Conventional radiography PVA: 5.3%	Grade 1+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Malgo 2017 Retrospective cohort	Adults referred for osteoporosis evaluation, N=552 (137/405)	67.5 years (10.1)	DXA with VFA	Conventional radiography PPA, Grade 2+: 24.4%	Grade 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Mazzaferro 2006 Cross-sectional	Adults on standard triple or double immunosuppressive therapy, N=53 (31/22)	45 years (12.0)	DXA with VFA	Conventional radiography PVA: 7.1%; PPA: 32.1%	Grade 1+ QM-MXA v VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Rea 2000B Cross-sectional	Postmenopausal women referred for osteoporosis evaluation, N=161	64.0 years (7.1), 49-81	DXA with VFA	Conventional radiography PVA: 10.1%; PPA: 34.6%	Grade 1+, 2+ Visual v VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR

Study Type of study	Population Number of participants (M/F)	Mean age (SD), range	Index test	Reference standard Prevalence of VF[a]	Fracture severity Definition of vertebral fracture	Outcomes
Rud 2016 Cross-sectional	Adults≥65 years-old referred for osteoporosis evaluation, N=235 (25/210)	74.9 years (6.9)	DXA with VFA	Conventional radiography PPA: 58.3%	Grade 1+, 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Schousboe 2006 Cross-sectional	Women≥65 years-old referred for BMD assessment or who have osteoporosis or osteopenia, N=204	74.2 years, 65-93	DXA with VFA	Conventional radiography PVA, Grade 2+: 1.1% PPA, Grade 2+: 7.9%	Grade 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Sullivan 2011 Prospective cohort	Men with non-metastatic cancer, N=116	75.0 years	DXA with VFA	Conventional radiography PPA: 32.8%	Grade 1+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR
Van Dort 2018 Retrospective cohort	Adults≥50 years-old participating in COPD-related osteoporosis trial, N=87 (50/37)	64.5 years (7.1)	DXA with VFA	Conventional radiography PVA: 8.1%; Chest CT PVA: 9.4%	Grade 1+, 2+ VSQ-G	• Sensitivity/specificity • PPV/NPV • PLR/NLR • AUC
Vokes 2003	Adults referred for BMD assessment, N=297 (25/272) recruited participants;	64.0 years (13) for recruited participants	DXA with VFA	Conventional radiography	Grade 2+ Visual then QM	• Sensitivity/specificity • PPV/NPV • PLR/NLR

Study Type of study	Population Number of participants (M/F)	Mean age (SD), range	Index test	Reference standard Prevalence of VF[a]	Fracture severity Definition of vertebral fracture	Outcomes
Prospective cohort	reported data is for N=66			PPA, Grade 2+: 32.3%		

Abbreviations: AUC, area under the curve; BMD, bone mineral density; CT, computed tomography scan; DXA, dual-energy X-ray absorptiometry; MRX, quantitative morphometric radiography; MXA, quantitative morphometric x-ray absorptiometry; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; PPA, per-person analysis; PVA, per-vertebra analysis; QM, quantitative morphometry; VFA, vertebral fracture assessment; VSQ-G, visual semi-quantitative method-Genant.

Notes:

a. Prevalence is for any vertebral fracture (grade≥1), unless otherwise stated, identified by the reference standard test.

b. Grade 1 fractures are mild, moderate, or severe vertebral fractures and are defined as any vertebra with a ≥20% decrease in height as determined by the method used to identify VF. Grade 2 fractures are moderate or severe vertebral fractures and defined as any vertebra with a ≥25% decrease in height.

1.1.6. Summary of the diagnostic evidence

Table 3: Clinical evidence summary: sensitivity and specificity for DXA with VFA compared to expert radiological assessment of conventional radiography – per-vertebra analysis

Studies	Number of evaluated vertebrae	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Certainty
Vertebral fractures, Grade 1+							
16 studies	37,858	Very serious[a]	Very serious[b]	Not serious	Not serious	Sensitivity=0.82 (0.72-0.90)	Very low
		Very serious[a]	Not serious	Not serious	Not serious	Specificity=0.98 (0.97-0.99)	Low
Vertebral fractures, Grade 2+							
10 studies	17,219	Very serious[a]	Very serious[b]	Not serious	Serious[c]	Sensitivity=0.76 (0.61-0.88)	Very low
		Very serious[a]	Not serious	Not serious	Not serious	Specificity=0.99 (0.98-1.00)	Low

a. Downgraded by 2 increments for risk of bias due to high risk in the majority of the evidence.

b. Downgraded by 2 increments for inconsistency (assessed by visual inspection of the forest and ROC plots).

c. Downgraded by 1 increment for imprecision because the 95% CI crossed 1 MID line (0.5, 0.7 for sensitivity and specificity).

Table 4: Clinical evidence summary: sensitivity and specificity for DXA with VFA compared to expert radiological assessment of conventional radiography – per-person analysis

Studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Certainty
Vertebral fractures, Grade 1+							
13 studies	3381	Very serious[a]	Very serious[b]	Not serious	Not serious	Sensitivity=0.87 (0.77-0.94)	Very low
		Very serious[a]	Serious[c]	Not serious	Not serious	Specificity=0.95 (0.88-0.98)	Very low
Vertebral fractures, Grade 2+							
8 studies	2391	Very serious[a]	Very serious[b]	Not serious	Not serious	Sensitivity=0.83 (0.72-0.92)	Very low
		Very serious[a]	Serious[c]	Not serious	Not serious	Specificity=0.94 (0.83-0.99)	Very low

a. Downgraded by 2 increments for risk of bias due to high risk in the majority of the evidence.
b. Downgraded by 2 increments for inconsistency (assessed by visual inspection of the forest and ROC plots).
c. Downgraded by 1 increment for inconsistency (assessed by visual inspection of the forest and ROC plots).

Table 5: Clinical evidence summary: sensitivity and specificity for DXA with VFA compared to expert radiological assessment of chest computed tomography – per-vertebra analysis

Studies	Number of evaluated vertebrae	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Certainty
Vertebral fractures, Grade 1+							
1 retrospective cohort study, N=87 (van Dort 2018)	640	Very serious[a]	Not serious[b]	Not serious	Serious[c]	Sensitivity=0.57 (0.43-0.69)	Very low
		Very serious[a]	Not serious[b]	Not serious	Not serious	Specificity=0.97 (0.95-0.98)	Low
Vertebral fractures, Grade 2+							
1 retrospective cohort study, N=87 (van Dort 2018)	640	Very serious[a]	Not serious[b]	Not serious	Serious[c]	Sensitivity=0.42 (0.23-0.63)	Very low
		Very serious[a]	Not serious[b]	Not serious	Not serious	Specificity=0.99 (0.98-1.00)	Low

a. Downgraded by 2 increments for risk of bias due to patient selection, reference standard and flow and timing.
b. Not applicable as outcome is from 1 study.

c. Downgraded by 1 increment for imprecision because the 95% CI crossed 1 MID line (0.5, 0.7 for sensitivity and specificity).

1.1.7. Economic evidence

Economic evidence related to VFA with DXA is considered as part of the evidence review in Section 1.2 below.

1.2. Review question: What is the clinical and cost-effectiveness of VFA with DXA (DXA scan) for identifying people with a vertebral fracture?

1.2.1. Introduction

Although vertebral fractures are a common type of fragility fractures, they are often not suspected and so few come to clinical attention. Vertebral fractures are a strong predictor of future fracture risk and are associated with significant morbidity, even when they do not present clinically, and are also associated with increased mortality.

1.2.2. Summary of the protocol

Table 6: PICO characteristics of review question

Population	Adults (18 years and older) who are having a dual-energy X-ray absorptiometry (DXA) assessment.
Intervention	Vertebral fracture assessment with DXA Followed by treatment: • Alendronate • Ibandronate • Risedronate • Abaloparatide • Denosumab • Raloxifene • Romosozumab • Teriparatide • Strontium ranelate • HRT (Newer forms)
Comparison	DXA only Followed by treatment: • Alendronate • Ibandronate • Risedronate • Abaloparatide • Denosumab • Raloxifene • Romosozumab • Teriparatide • Strontium ranelate • HRT (Newer forms)
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:

	• Vertebral fracture
	• Generic health-related quality of life (continuous outcomes will be prioritised [validated measures]). The hierarchy for extracting will be as follows, if measures higher on higher on hierarchy are reported others will not be:
	  ○ EQ-5D
	  ○ SF-6D
	  ○ SF-36
	  ○ SF-12
	  ○ Other utility measures (AQOL, HUI, 15D, QWB)
	• Health-related quality of life measure for vertebral fractures (QUALEFFO-41)
	• Change in management.

Study design	• Diagnostic randomised controlled trials (RCTs). • Published NMAs and IPDs will be considered for inclusion. • Systematic reviews of randomised controlled trials.

1.2.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.2.4. Effectiveness evidence

1.2.4.1. Included studies

No studies were identified for inclusion in the evidence review. See evidence study selection in Appendix C.

1.2.4.2. Excluded studies

See the excluded studies listed in Appendix K.

1.2.5. Summary of studies included in the effectiveness evidence

No studies were identified for inclusion in the evidence review.

1.2.6. Summary of the effectiveness evidence

No studies were identified for inclusion in the evidence review.

1.2.7. Economic evidence

For methods see the health economic review protocol in Appendix A.

1.2.7.1. Included studies

One health economic study with the relevant comparison was included in this review (Clark 2014). This is summarised in Table 7 below and the health economic evidence table in Appendix I.

See also the health economic study selection flow chart in Appendix H.

1.2.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations, as detailed in Appendix K.

1.2.8. Summary of included economic evidence

Table 7: Health economic evidence profile: VFA plus DXA versus DXA

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	ICER	Uncertainty
Clark 2014 (UK)	Partially applicable[a]	Potentially serious limitations[b]	• Cost-utility analysis (QALYs) • Decision tree capturing the additional number of people treated as a result of VFA. • Population: ○ Fracture cohort: Women over 50 years attending for DXA after a low trauma fracture as part of FLS ○ Primary care cohort: Women from primary care aged 65-80 years identified as being at high risk of having had a vertebral fracture • Scenarios: 1. NOGG pathway (treatment based on age-dependent FRAX risk thresholds in NOGG guideline) 2. 20/3 pathway (treatment if FRAX risk of MOF 20% or hip fracture 3%) • Interventions: 1. No VFA (treatment based on FRAX risk) 2. VFA (treatment based on FRAX risk plus treatment in those with vertebral fracture who were not otherwise treated) • Time horizon: 5 years	NR[c]	NR	Fracture cohort (intervention 2 versus 1)[d] Scenario 1: £2,130 per QALY gained Scenario 2: £3,243 per QALY gained Primary care cohort (intervention 2 versus 1)[d] Scenario 1: £7,831 per QALY gained Scenario 2: Dominant	No probabilistic analysis. In sensitivity analyses, ICERs for VFA ranged from being dominant (cost saving with higher QALYs) to £150,222 per QALY gained.

Abbreviations: DXA= dual-energy X-ray absorptiometry; FLS= fracture liaison service; FRAX= fracture risk assessment tool; ICER= incremental cost-effectiveness ratio; MOF= major osteoporotic fracture; NOGG= National Osteoporosis Guideline Group; QALY= quality-adjusted life years; RCT= randomised controlled trial; VFA vertebral fracture assessment

(a) 2011 cost year and VFA costs informed by US Medicare costs may not reflect current NHS context. It is not stated whether costs and health outcomes were appropriately discounted over the model time horizon. Utilities methods fully aligned with NICE reference case.

(b) Decision tree may not be the most appropriate model structure for osteoporosis. Time horizon of 5 years is not sufficiently long to capture lifetime effects of outcomes such as fracture. Some relevant costs may be omitted e.g. residential care. Effectiveness of intervention under consideration estimated based on a retrospective cohort. Neither total nor incremental costs and QALYs were reported, only ICERs. Probabilistic analysis was not undertaken.

(c) 2011 UK pounds. Cost components incorporated: Cost of VFA, medication costs (excluding calcium and vitamin D), treatment treatment-related adverse event costs. Fracture costs varied by fracture type and included length of inpatient stay, surgery, physiotherapy, and outpatient follow-up.

(d) Authors 'best estimate' results with medication costs assuming most are on calcium/vitamin D supplements already, reduced cost of VFA (£15) assuming increased use of modern scanners and poor adherence resulting in only 17.5 % fracture reduction over 5 years.

1.2.9. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2.10. Unit costs

Relevant unit costs are provided in **Table 8** below to aid consideration of cost-effectiveness. Note that the NHS National Cost Collection does not report separate costs for DXA with and without VFA. Spinal radiographs, typically undertaken using x-ray, may be used to confirm vertebral fracture following a positive VFA.

Table 8: Unit costs associated with diagnostic imaging

Resource	Unit costs	Source
DXA scan	£84[(a)]	NHS National Cost Collection 2023/24
Plain film (x-ray)	£43.72[(b)]	

(a) Weighted average cost of DXA (Currency code RD40Z). This includes aggregated DXA costs and will include those with and without VFA.
(b) Weighted average cost of plain film.

1.2.11. Evidence statements

1.2.12. Economic evidence statement

One cost-utility analysis (with a 5-year time horizon) evaluated the use of VFA in women aged 50 years and over attending DXA following a low-trauma fracture, as part of a fracture liaison service. The study found that supplementing the NOGG pathway with VFA to identify vertebral fractures in individuals who would otherwise not initiate treatment was cost effective (ICER: £2,130 per QALY) compared to using the NOGG pathway alone using a threshold of £20,000 per QALY gained. Similarly, adding VFA to the 20/3 treatment pathway (treatment if FRAX risk of major osteoporotic fracture ≥20% or hip fracture ≥3%) was cost effective (ICER: £3,243 per QALY) compared to using the 20/3 threshold alone.

Additionally, in women aged 65–80 years from primary care identified as high risk for prevalent vertebral fracture using the COSHIBA tool, incorporating VFA into both the NOGG and 20/3 pathways was also cost effective (ICER of £7,831 per QALY and dominant [lower cost and higher QALYs], respectively) compared to not adding VFA using a threshold of £20,000 per QALY gained. The study did not include probabilistic analysis. Overall, it was assessed as partially applicable with potentially serious limitations.

1.3. The committee's discussion and interpretation of the evidence

1.3.1. The outcomes that matter most

1.3.1.1. Diagnostic accuracy of DXA with VFA

The committee considered sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive values, and area under the curve to be the most important outcomes for this review. Discrimination data is important to correctly classify individuals into risk groups to inform decision of further interventions.

The guideline committee considered sensitivity the most important measure for this tool to minimise the risk of false negative results. False negative results would mean that vertebral fractures would be missed and that people with them would not be offered appropriate treatment, which could increase subsequent fractures and reduce quality of life. Specificity was also considered important to prevent unnecessary imaging and treatment, which would have health (exposure to radiation) and resource implications.

The studies reported accuracy using a per-vertebra or per-person analysis which have both been reported separately. The per vertebra analysis was considered more important in the accuracy evidence as the VFA could accurately identify any VF scanned. The per-person analysis was considered important clinically as the ability to identify that a patient has one or more vertebral fractures will often change their management. Both types of analysis were included in the review to maximise the evidence as studies may only report one type of analysis. Most studies reported sufficient data to calculate diagnostic test accuracy for Grade 1 and above (often described in the studies as 'minor', 'moderate', and 'severe') vertebral fractures and for Grade 2 and above ('moderate' and 'severe') vertebral fractures only.

Reflecting the different populations assessed in the studies, the prevalence in the included studies comparing DXA with VFA to expert radiological assessment of conventional radiographs varied greatly. Meta-analysis of positive and negative predictive values for the available per-vertebra and per-person analyses was not conducted due to the variation in prevalence in the studies (ranging from 1.1% to 46.5% for the former, and from 6.8% to 58.3% for the latter). Meta-analysis of positive and negative likelihood ratios was also not conducted given the variation in pre-test risk of vertebral fracture for people eligible for DXA assessment. Meta-analysis of the AUC statistic was not conducted as there were only two studies (Bazzocchi 2012, van Dort 2018) that reported it.

1.3.1.2. Diagnostic test and treat of DXA with VFA

Vertebral fracture, generic health related quality of life, health related quality of life measures for vertebral fractures and change in management were considered by the guideline committee to be equally important for decision making and were therefore all rated as critical. No evidence was identified for any of the outcomes.

1.3.2. The quality of the evidence

1.3.2.1. Diagnostic accuracy of DXA with VFA

In the meta-analysis of the per-vertebra analysis, the certainty was low for specificity due to very serious risk of bias and very low for sensitivity due to very serious risk of bias and inconsistency (and imprecision for Grade 2 fractures). The meta-analysis of the per-person analysis had very low certainty for sensitivity and specificity due to very serious risk of bias and inconsistency.

Most evidence was assessed to be at very serious risk of bias because the studies were at high risk of bias for the following domains: patient selection (including inappropriate exclusions), index test (lack of details about VFA assessment), reference standard (concerns about expertise of assessor) and timing and flow (DXA with VFA conducted at different time to conventional radiography).

Sensitivity for both analysis types and fracture severities were downgraded due to very serious inconsistency. Visual inspection of the forest plots and ROC curves revealed substantive inconsistency. The specificity outcomes were downgraded for serious inconsistency in the per-person analysis but not for the per-vertebra analysis. Prespecified subgroup analysis to explore heterogeneity in the results was conducted for type of VFA scan (single-energy, dual-energy) but did not explain the inconsistency. Subgroup analysis by expertise of the assessor of the reference standard was not possible as it was clear that trained experts were used in all but two of the studies. The committee discussed the likelihood that the heterogeneity was caused by the high range in prevalence across the studies.

Sensitivity for Grade 2 per-vertebra analysis was downgraded for imprecision due to the confidence intervals crossing the decision thresholds of 0.7 and 0.5, above and below which a test would or would not be recommended.

Nine studies were conducted in adults referred for BMD or osteoporosis evaluation, whilst 15 studies were conducted in specific populations (for example, postmenopausal women and adults over 65 years-old) or in people with conditions (for example, rheumatoid arthritis) or on medication (for example, immunosuppressants) that are known to adversely affect bone mineral density. The committee agreed that all these population types were appropriate and should not be downgraded for population indirectness.

Most studies used conventional radiography as the reference standard, but one retrospective cohort study in osteoporotic adults with moderate-to-severe COPD was identified that used CT. The per-vertebra prevalence in adults participating in this study was 9.4% for Grade 1+, and 4.1% for Grade 2+ vertebral fractures. The certainty of evidence for both sensitivity and specificity was low to very low. Both outcomes were downgraded due to concerns about patient selection, and the flow and timing of the index and reference tests with an average time between DXA with VFA and conventional radiography or chest CT of greater than 5 months. Sensitivity was further downgraded due to serious imprecision.

1.3.2.2. Diagnostic test and treat of DXA with VFA

No studies were identified that assessed the effectiveness of DXA with VFA to identify vertebral fracture.

1.3.3. Benefits and harms

1.3.3.1. Diagnostic accuracy of DXA with VFA

The committee agreed using their knowledge and experience that both per-vertebra and per-person analyses were important to understand the accuracy of DXA with VFA to identify VF with a per-vertebra analysis indicating how accurate it is in identifying whether a vertebra is fractured and a per-person analysis indicating how accurate it is in identifying whether a person has a vertebral fracture.

In the per-vertebra analysis for the identification of any grade (severity) of vertebral fracture, meta-analysis of 16 studies suggested that there was good sensitivity (0.82 [95%CI 0.72 to 0.90]), although there is substantive uncertainty. The per-vertebra prevalence for the included studies ranged from 1.7% to 46.5% for Grade 1+ vertebral fractures. Meta-analysis of 10 studies for the diagnosis of Grade 2+ vertebral fractures showed that sensitivity is

slightly reduced to 0.76 (95%CI 0.61 to 0.88). The prevalence of Grade 2+ vertebral fractures in these studies ranged from 1.1% to 29.3%.

In the per-person analysis, meta-analysis of 13 studies suggested that it may have good sensitivity in identifying people with any type of vertebral fracture with a point estimate of 0.87 (95%CI 0.77 to 0.94), although there is some uncertainty. The per-person prevalence for the included studies ranged from 11.3% to 58.3%. For the identification of people with Grade 2+ vertebral fractures, meta-analysis of 8 studies suggests that it may have good sensitivity of 0.83 (95%CI 0.72 to 0.92) although there was some uncertainty. The prevalence of Grade 2+ vertebral fractures ranged from 6.8% to 34.9%.

The specificity of DXA with VFA was very high with the point estimates for the per-person and per-vertebra analyses both greater than 0.9. The 95% CIs for the per-vertebra analyses were narrow for the identification of a Grade 1 or worse vertebral fracture, indicating a low probability of misidentifying a vertebra as fractured (that is, a false positive). However, the 95% CIs for the per-person analysis were relatively wide (especially for identification of Grade 2 or worse fractures), reflecting the variability in the results (that is, inconsistency) of the individual studies. This shows some uncertainty in identifying people with a Grade 1+ (95%CI 0.88 to 0.98) or Grade 2+ VF (95%CI 0.83 to 0.99). This means, for example, that when identifying people with Grade 2+ fractures, anywhere from 17 to 1 person out of 100 could be misidentified as having a VF.

One retrospective cohort study (van Dort 2018), which was conducted in 87 osteoporotic adult's over-50 years-old who were participating in a COPD-related trial, was identified that used chest CT and conventional radiography as reference standards. The sensitivity of DXA with VFA was very low for the diagnosis of grade 1+ vertebral fractures (0.57 and 0.51. respectively, for CT and conventional radiography as reference standards). Although these estimates are from only one small study (640 evaluable vertebrae) in a population at high risk of vertebral fracture, this suggests that DXA with VFA would result in a high number of missed vertebral fractures (false negatives). The specificity was very high with a point estimate of 0.97 and 0.99 for Grade 1+ and Grade 2+ fractures, respectively. The small number of false positives suggests that the risk of misdiagnosing vertebral fractures of any grade severity using DXA with VFA rather than chest CT would be negligible.

1.3.3.2. Diagnostic test and treat of DXA with VFA

No studies were identified that assessed the effectiveness of DXA with VFA to identify vertebral fracture.

1.3.4. Committee conclusions

The committee recommended that VFA should be considered in all people aged 50 and over who are receiving a DXA scan. The addition of VFA to DXA is quick in practice (adding approximately 6 minutes to a DXA scan), does not require additional visits, and could reduce reliance on conventional radiography (and therefore exposure to higher doses of ionizing radiation) to identify vertebral fractures. The age limit of 50 was in line with the recommendations on risk factors (Evidence review A) and the management pathway including the use of risk prediction tools (Evidence review C), BMD (Evidence review D), and their effectiveness (Evidence review E). This would provide additional opportunity to identify vertebral fractures when conducting DXA imaging.

Vertebral fractures, which are the most common type of osteoporotic fracture, are normally identified in clinical practice using semi-quantitative analysis of conventional radiography, one of the gold standards for identifying VFs. Given the exposure to ionising radiation, conventional radiography is typically performed only if it would change management and when the VF is symptomatic (for example, when there is back pain) or when confirming a positive VFA. However, most VFs are underdiagnosed because in many cases symptoms

are not considered to be due to VF and they are not subsequently imaged. DXA, which is relatively widely available, uses a lower dose of ionising radiation compared to conventional radiography to image the spine and provides additional information on bone health

The evidence suggested that the use of DXA with VFA had a relatively low risk of misdiagnosing vertebral fractures with high specificity reported for both per-vertebra and per-person analyses, although there was some uncertainty with the latter analysis. However, the point estimates were above the agreed threshold of 0.7 that the committee considered to be a reasonable level to make a recommendation, the committee recognised that the risk of misidentification (false positives) of a Grade 1 (or 2) or worse fracture is greater when a per-person analysis is used and some people would likely be misidentified (1-3% for PVA compared to 1-17% for PPA). The per vertebra analysis was considered more important in the accuracy evidence as the VFA could accurately identify any VF scanned.

By contrast, there was some risk of missing Grade 1+ VFs on both a per-vertebra and per-person analysis (sensitivity of 0.82 and 0.87 respectively) and Grade 2+ VFs (sensitivity of 0.76 and 0.83 respectively). This was also above the agreed threshold of 0.7 that the committee considered to be a reasonable level to make a recommendation. However, the committee were aware that this would still mean that a substantial number of people (13-18%) with vertebral fractures would be missed.

Reflecting the risk factor recommendations (see Evidence review A), the committee also agreed that doing a VFA when doing a DXA should be considered in people under the age of 50 at high risk of VF, including those with any of the following risk factors:

- a previous major osteoporotic fracture
- signs or symptoms of vertebral fracture for example, back pain or radiating rib pain, change in body shape (such as height loss, or changes suggestive of spinal deformity such as rounded shoulders, exaggerated kyphosis) or suspicion of VF from the DXA scan
- current or frequent user of systemic glucocorticoids
- exceptionally low BMD for their age from DXA.

The committee recognised that some height loss occurs naturally with age and that it is difficult to define a specific threshold for height loss indicative of vertebral fracture. The committee agreed that a historical height loss of >4 cm (which could be self-reported) would merit investigation for VF. The committee agreed this threshold as a height loss under 4 cm would not be able to discriminate between vertebral fracture or other spinal injury. The committee also discussed that a lower threshold of height loss would be acceptable when a recent height loss reading was recorded between serial DXA scans. The International Society for Clinical Densitometry (ISCD) uses a historical height loss threshold of greater than 4cm/6cm, and prospective height loss threshold of greater than 2cm/3cm on serial DXA scans, for postmenopausal women/men compared to young adulthood.

The committee discussed circumstances when a VFA should not be performed whilst conducting a DXA scan. The committee agreed that specifying when DXA may not be appropriate was important because not all clinicians may know about the technical requirements for DXA. The reasons included when the person has had spinal imaging in the last 3 months and has no recent symptoms of vertebral fracture. Additionally, technical issues (for example, the person's size is greater than the ability of the scanner to view the image); and the presence of scoliosis (which can result in poor image quality of vertebrae). The committee also discussed Scheuermann's disease which can make it difficult to distinguish fractured vertebra from the wedged vertebra that are a feature of the disease. However, this was not included in the recommendation as it cannot be seen on DXA while scoliosis can.

Given the low risk of misdiagnosing Grade 1+ and Grade 2+ VFs, the committee agreed that a positive result on VFA would in most cases be sufficient to diagnose VF and that spinal

radiography should only be subsequently considered if this would change patient management. This was supported by the high specificity in the per vertebra analysis with the lowest CI at 0.97. The per vertebra analysis was considered more important in the accuracy evidence as the VFA could accurately identify any VF scanned. Nevertheless, the committee recognised that further spinal imaging investigations may be needed in some cases. For example, spinal radiography may be needed if there is a negative result despite the persistence of symptoms, whilst an MRI may be needed to estimate the recency of fracture if its age is not known. Therefore, a recommendation was made that spinal imaging should not routinely be done after a positive VFA to confirm the fracture.

From a patient perspective it is important to know whether you have any new vertebral fractures. It is also beneficial to have all relevant scans on the same visit rather than having a DXA scan and then needing to return for further VFA scans. It was noted that scans should be analysed immediately to ensure patients did not leave before checking they were readable.

1.3.4.1. Research recommendation

A research recommendation was made on the diagnostic accuracy of DXA-based VFA scans using the newer generation scanners. The committee discussed the importance of this research to determine if newer generation scanners improved the accuracy of identifying VFs.

1.3.5. Cost effectiveness and resource use

One UK economic evaluation was identified for this review, which compared vertebral fracture assessment (VFA) with no VFA in women over 50 years attending a fracture liaison service for a DXA scan following a low-trauma fracture (fracture cohort), and women from primary care aged 65-80 years identified as being at high risk of having had a vertebral fracture using the COSHIBA screening tool (primary care cohort). The analysis was performed within two treatment pathways:

1. The current NOGG treatment pathway (which has age-dependent FRAX risk thresholds for treatment), and

2. Setting FRAX treatment thresholds of a 20% 10-year risk for major osteoporotic fractures and a 3% risk for hip fractures.

The model was informed by an analysis of UK patient cohorts where everyone was given VFA at the time of DXA and asked to provide information to estimate fracture risk using the FRAX risk calculator. The proportion of women who would be treated based on FRAX fracture risk was calculated in each treatment pathway. Change in clinical management following VFA was defined as a vertebral fracture in a patient who would not otherwise be treated based to their fracture risk as it was assumed that people identified as having a vertebral fracture would be recommended treatment. The impact of this change in management was then modelled by estimating fractures avoided through additional treatment.

The analysis found that the addition of VFA to DXA was cost effective in both populations, irrespective of the treatment pathway being used. In the fracture cohort, the study reported a cost per QALY gained of £2,130 and £3,243, for the 20/3 pathway and the NOGG pathway analyses, respectively. In the primary care cohort, this was £7,831 per QALY gained with the 20/3 pathway and cost saving and more effective with the NOGG pathway.

The committee noted that the clinical study informing the analysis was excluded from the clinical review looking at the clinical and cost-effectiveness of VFA because it was non-randomised. However, as it reflected UK practice, included relevant populations, and

examined treatment pathways such as the NOGG pathway, the committee considered it suitable for inclusion within the health economic review. The study's primary outcome was initiation of alendronate following identification of vertebral fracture using VFA. The model assumed perfect identification of vertebral fractures and applied a treatment effect to all individuals starting treatment. Sensitivity analyses indirectly explored the impact of misdiagnosis on the ICER by applying stricter diagnostic criteria, which reduced the number of people eligible for treatment after VFA. Across these analyses, the cost per QALY gained with VFA consistently exceeded £20,000 (ranging from £20,843 to £150,222), indicating that diagnostic accuracy - defined here as minimising false positives - was an important driver of VFA's cost-effectiveness.

The committee noted that the cost of VFA (£24) in the analysis was sourced from Medicare in the USA; however, in the primary analysis they used a reduced cost of £15 to reflect the availability of newer scanners that do not need patient repositioning, thereby reducing the process time with VFA. The committee agreed this was likely to be a reasonable estimate to reflect the cost of additional time associated with performing, reviewing, and reporting VFA scans. They discussed that there would be a small amount of additional time required to perform a VFA scan when doing a DXA and agreed this could take up to 6 minutes. They also agreed there would be some additional time required to review and report VFA images. This was estimated to vary depending on the number of fractures present, typically ranging from 1 to 5 minutes, with an average of 2 to 3 minutes for each. The person reviewing the images could be a radiographer, radiologist, or a non-radiology clinician with a special interest in osteoporosis. They also noted that most modern scanners are already equipped to perform VFA, meaning no additional capital investment would be necessary.

The committee noted that the cost-effectiveness analysis did not include any costs related to spinal radiographs. If a spinal radiograph is required to confirm a vertebral fracture diagnosis from VFA this will be an additional downstream cost associated with the VFA comparator. They discussed that practice varies but that, in some areas, a significant proportion of individuals referred for VFA scans are also referred for confirmatory spinal radiographs currently; however, the committee agreed this was not necessary in most cases and made a recommendation within the guideline against routinely performing confirmatory spinal radiographs in patients with a positive vertebral fracture diagnosis following VFA. In addition, they discussed that if some people in the population would have been referred for spinal radiograph in additional to DXA as part of their assessment in the absence of VFA, use of VFA alongside DXA would displace the need for spinal radiograph at lower cost. The committee believed this group would be minimal, as the primary advantage of VFA over radiography is reduced radiation exposure. Therefore, in the absence of VFA, it is unlikely that other imaging would be conducted in most people having DXA.

The committee highlighted that the model assumed all patients began treatment with oral bisphosphonates, but that in current practice a range of treatments are available, in particular anabolic therapies that may be appropriate for people that have had a vertebral fracture. The modelled benefit of adding VFA was that more people would start treatment that would not otherwise due to identification of vertebral fractures. A further potential benefit, not captured in the analysis, is that people already eligible for treatment on other grounds may be suitable for anabolic treatment once a vertebral fracture is confirmed.

It was noted that a 5-year time horizon was used, which may not fully capture long-term costs and health benefits, particularly the occurrence of subsequent fractures, which would likely underestimate the true cost-effectiveness of the intervention.

The committee also highlighted that the COSHIBA screening tool used to identify people at high risk of vertebral fracture in the primary care cohort is not used in current practice and that currently clinical judgement would be used.

The committee noted that in some sensitivity analyses, VFA was no longer cost-effective. In the base-case analysis, vertebral fractures were identified using six-point quantitative morphometry (QM), with a height reduction of 25% or more used as the diagnostic criterion. Sensitivity analyses using a 30% height reduction instead resulted in VFA no longer being cost effective; however, the committee noted that 25% was the standard definition for grade 2 fractures. Sensitivity analysis implementing an algorithm-based qualitative (ABQ) assessment also resulted in VFA no longer being cost effective (ICER of £150,222 and £92,912 in the fracture and primary care cohorts, respectively). The committee reviewed the data underpinning the cost-effectiveness of both methods. They noted that using ABQ, the analysis suggested that three individuals would change pharmacological management who otherwise would not in both the primary care (n=251) and fracture cohorts (n=377). These numbers were 12 and 21, respectively, with QM. When considering the use of these methods in current care, the committee noted that most VFA readings are uncomplicated in nature making the whole process semi-autonomous, somewhat akin to QM. A minority of readings require further investigation and review, similar in nature to the ABQ process, though they noted ABQ is not frequently utilised as a process. They considered the cost-effectiveness of VFA to more likely be represented by the primary analysis with QM.

Overall, the committee agreed that the published cost-effectiveness evidence supported that the addition of VFA to DXA may be cost-effective in people 50 years and over with fracture having DXA and people aged 65 to 80 years at high risk of vertebral fracture having DXA, with some uncertainty present. They noted there was no cost-effectiveness evidence for VFA in everyone over 50 years attending for DXA that their recommendations encompassed and that the populations not covered (people without fragility fracture and under 65 or not considered at high risk of vertebral fracture) are likely to have a lower prevalence of undiagnosed vertebral fractures which may result in VFA being less cost-effective. However, the committee agreed that due to current low identification rates of vertebral fractures this approach was likely to increase treatment in people sufficiently to justify the additional costs of VFA and would improve downstream health outcomes through reducing the incidence of future fragility fractures. The committee also observed that no cost-effectiveness evidence is available for people under 50 years. While the overall risk of vertebral fracture in this group is low, they identified specific sub-groups at higher risk in whom the benefits of VFA are expected to be comparable to those over 50. They further noted that these sub-groups represent only a small proportion of people under 50 undergoing DXA, who themselves constitute a small proportion of the overall DXA population.

The committee also discussed whether their new recommendations for use of VFA with DXA would result in a change in practice that would have a substantial resource impact to the NHS in England. They highlighted that current use of VFA with DXA is variable, with most common practice appearing to be using it in selected groups of people but that some areas do not currently use it at all. The recommendation for use of VFA in all people having DXA over 50 would therefore be a change in practice. They also agreed that practice following VFA was variable currently and that in some areas it is common to do spinal radiography to confirm VFA. In these areas the recommendation to not routinely do this will also be a change in practice.

The committee agreed that this change in practice is likely to result in increased costs associated with the additional staff time to perform, review and report VFA. These costs are relatively small per scan but will apply to most people having DXA. There may also be additional staff training costs to enable expanded access. Increased capital investment was not anticipated as current DXA machines have the capacity to undertake VFA.

In groups where VFA is currently in use, a reduction in confirmatory spinal radiographs is anticipated due to the new recommendation to not routinely do spinal imaging after positive VFA. Where VFA is not currently in use, the number of referrals for spinal radiographs may increase slightly as a small proportion of results may require subsequent spinal radiograph where there is uncertainty. A third group considered in the discussion included individuals

who receive spinal radiographs as an alternative to VFA, rather than as a follow-up test: in these cases, VFA would displace spinal radiograph at lower cost. The committee concluded that their recommendations regarding VFA and spinal imaging would likely lead to a net decrease in the number of spinal radiographs performed compared to current practice and this would offset a sizeable portion of the additional costs of VFA.

Increased use of VFA in the NHS is expected to increase identification of vertebral fractures as these are often missed currently. This is expected to result in increased treatment and better targeted treatment that will reduce subsequent fractures, thereby reducing downstream healthcare costs associated with fractures and improving patient outcomes.

The committee concluded that the overall financial impact of the new recommendations on the NHS would likely not be significant over the long term.

1.3.6. Other factors the committee took into account

The committee acknowledged that most evidence for the accuracy of DXA-based VFA was in postmenopausal women and that men and people with learning or physical disabilities are underrepresented. The committee also noted that people with learning disabilities could struggle with the positioning needed for the DXA and DXA-based scan.

1.3.7. Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1-1.5.4 and the research recommendation on the diagnostic accuracy of DXA-based VFA scan or imaging for identifying vertebral fractures.

1.4. References

1.4.1. Included studies for review question: What is the diagnostic accuracy of DXA-based VFA scan or imaging for identifying people with a vertebral fracture?

1.4.1.1. Diagnostic accuracy

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result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 14(11): 871-8

1.4.1.2. Economic

Economic evidence related to VFA with DXA is considered as part of the evidence review in section 1.2.7.

1.4.2. Included studies for review question: What is the clinical and cost-effectiveness of VFA with DXA (DXA scan) for identifying people with a vertebral fracture?

1.4.2.1. Effectiveness

No relevant studies were identified for this evidence review.

1.4.2.2. Economic

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Appendices

Appendix A Review protocols

A.1 Review protocol for the diagnostic accuracy of DXA with vertebral fracture assessment (VFA) for identifying vertebral fractures

Field	Content
Review title	Diagnostic accuracy of DXA with vertebral fracture assessment (VFA)
Review question	What is the diagnostic accuracy of DXA with vertebral fracture assessment (VFA) for identifying vertebral fractures?
Objective	The review aims to assess the diagnostic accuracy of DXA with VFA compared to expert radiological assessment of conventional radiography or other imaging modalities.
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies Other searches:

	• Reference searching • Citation searching • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Osteoporosis or people at risk of vertebral fractures. Vertebral fractures are a common type of fragility fracture, yet they are often not suspected so a significant proportion go undiagnosed. Vertebral fractures are a strong predictor of future fracture risk and are associated with significant morbidity, even when they do not present clinically and are associated with increased mortality.
Population	Inclusion: • Adults (18 years and older) who are having a DXA assessment. Exclusion: • Children and young people less than 18 years.
Test	• Vertebral fracture assessment (VFA) with DXA scan
Reference standard	• Expert radiological assessment (explicit description of how the decision to label something as a vertebral fracture is necessary)
Types of study to be included	• Diagnostic: cohort and cross-sectional studies will be included.

Other exclusion criteria	• Non-English language studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. • Case-control studies
Context	All settings.
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. Accuracy of estimation of vertebral fracture: • Sensitivity/specificity • Likelihood ratio • Positive predictive value/negative predictive value • Area under the curve (AUC)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data, and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.

Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Diagnostic test accuracy studies: QUADAS-2	
Strategy for data synthesis	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.	
Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • VFA by DXA scan: single- or dual-energy scan • Expertise of the operator/interpreter of results (specialist versus non-specialist)	
Type and method of review	☐	Intervention
	x	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)

Language	English		
Country	England		
Anticipated or actual start date	July 2024		
Anticipated completion date	November 2025		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact Centre for Guidelines, NICE 5b Named contact e-mail osteoporosis@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		

Review team members	Carlos Sharpin, Guideline Lead Clare Jones, Senior Technical Analyst Linyun Fou, Technical Analyst Kate Lovibond, Health Economics Adviser Muksitur Rahman, Health Economist Sarah Glover, Information Scientist
Funding sources/sponsor	Development of this systematic review is being funded by NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website. https://www.nice.org.uk/guidance/indevelopment/GID-NG10216
Other registration details	N/A
Reference/URL for published protocol	N/A

Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Computed tomography; DXA; Diagnostic test; DXA; MRI; radiography; vertebral fracture assessment; VFA; X-ray.	
Details of existing review of same topic by same authors	N/A	
Current review status	☐	Ongoing
	x	Completed but not published
	☐	Completed and published
	☐	Completed, published, and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

A.2 Review protocol for the clinical and cost effectiveness of DXA with VFA for diagnosis of vertebral fracture

Field	Content
Review title	Clinical and cost-effectiveness of DXA with VFA for diagnosis of vertebral fracture
Review question	What is the clinical and cost-effectiveness of VFA with DXA (DXA scan) for identifying people with a vertebral fracture?
Objective	This is a review of review of test-and-treat studies to compare VFA with DXA (DXA) scan compared to DXA alone.
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies Other searches: • Reference searching • Citation searching • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.

	Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition	Osteoporosis or people at risk of vertebral fractures. Vertebral fractures are a common type of fragility fractures yet they are often not suspected and so few come to clinical attention. Vertebral fractures are a strong predictor of future fracture risk and are associated with significant morbidity, even when they do not present clinically and are associated with increased mortality.
Population	Inclusion: • Adults (18 years and older) who are having a DXA assessment. Exclusion: • Children and young people less than 18 years.
Intervention	• Vertebral fracture assessment (VFA) with DXA (DXA scan) Strata: targeted VFA vs everyone getting VFA Followed by treatment: Treatments: • Alendronate • Ibandronate • Risedronate • Abaloparatide • Denosumab • Raloxifene • Romosozumab • Teriparatide • Strontium ranelate • HRT (Newer forms)

Comparator	• DXA alone Followed by treatment. Treatments: • Alendronate • Ibandronate • Risedronate • Abaloparatide • Denosumab • Raloxifene • Romosozumab • Teriparatide • Strontium ranelate • HRT (Newer forms)
Types of study to be included	• Diagnostic randomised controlled trials (RCTs). • Published NMAs and IPDs will be considered for inclusion. • Systematic reviews of randomised controlled trials: For a systematic review (SR) to be included it must be conducted in line with the methodological processes described in the NICE manual. If sufficient details are provided, reviewers will either include the SR fully or use it as the basis for further analyses where possible. If sufficient details are not provided to include a relevant SR, the review will only be used for citation searching. Exclusion: • Non-randomised studies.
Other exclusion criteria	• Non-English language studies • Non-comparative cohort studies • Before and after studies • Conference abstracts

Context	All settings where NHS-funded care or social care is provided or commissioned.

Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	• Vertebral fracture
	• Generic health-related quality of life (continuous outcomes will be prioritised [validated measures]). The hierarchy for extracting will be as follows, if measures higher on hierarchy are reported others will not be:
	  ○ EQ-5D
	  ○ SF-6D
	  ○ SF-36
	  ○ SF-12
	  ○ Other utility measures (AQOL, HUI, 15D, QWB)
	• Health-related quality of life measure for vertebral fractures (QUALEFFO-41)
	• Change in management.

Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion.

	A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data, and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects If sufficient data is available, meta-regression or NMA-meta-regression will be conducted. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency, and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/

Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • VFA by DXA: single- or dual-energy scan • Expertise of the operator/interpreter of results (specialist versus non-specialist)		
Type and method of review	☒	Intervention	
	☐	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	July 2024		
Anticipated completion date	August 2025		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑

	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact Centre for Guidelines, NICE 5b Named contact e-mail osteoporosis@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
Review team members	Carlos Sharpin, Guideline Lead Clare Jones, Senior Technical Analyst Linyun Fou, Technical Analyst Kate Lovibond, Health Economics Adviser Muksitur Rahman, Health Economist		

	Sarah Glover, Information Scientist
Funding sources/sponsor	Development of this systematic review is being funded by NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/GID-NG10216
Other registration details	N/A
Reference/URL for published protocol	N/A
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	DXA; DEXA; randomised controlled trial; RCT; test-and-treat; vertebral fracture assessment; VFA

Details of existing review of same topic by same authors	N/A	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published, and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

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A.3 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions in the guideline update.
Search criteria	• Populations, interventions, and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A global health economic study search will be undertaken for the guideline update using population-specific terms and a health economic study filter – see Appendix B below. Note that this guideline is being consulted on in two parts, but the health economic search covered the full guideline health economic review.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2009 (including those included in the previous guideline), abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published 2009 onwards that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual. **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable,' with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies

	excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2009 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2009 will be rated as 'Not applicable'. • Studies published before 2009 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.(NICE2014) For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

- Q4.2a What is the diagnostic accuracy of DXA with vertebral fracture assessment (VFA) for identifying vertebral fractures?
- Q4.2b What is the clinical and cost-effectiveness of VFA with DXA (DXA scan) for identifying people with a vertebral fracture?

Table 9: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 17 June 2024	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 17 June 2024	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 202 Issue 6 of 12 CENTRAL to 2024 Issue 6 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 17 June 2024	Systematic review studies Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1	exp Densitometry/
2	(densitometr* or BMD-test* or BMD-tool* or densimetr*).tw.
3	(bone adj4 mineral adj4 dens* adj4 test*).tw.
4	(bone adj4 mineral adj4 dens* adj4 tool*).tw.
5	(absorptiometr* adj4 (dpx* or dual-energ* or dual-photon* or photon*)).tw.
6	(DXA* or DXA).tw.
7	or/1-6
8	Spinal Fractures/
9	((spin* or vertebr* or neck or cervical or lumbar or sacral or thoracic or coccy* or cord or backbone* or back) adj4 (fracture* or compress*)).tw.
10	(compress* adj4 fracture*).tw.
11	(VCF or VFA* or IVA* or LVA* or DVA* or MXA*).tw.
12	((instant or lateral or densitometric or morphometric or dual-energ*) adj4 (vertebr* adj4 assess*)).tw.
13	(physician* adj4 viewer*).tw.
14	or/8-13
15	7 and 14
16	animals/ not humans/
17	15 not 16
18	limit 17 to english language
19	limit 18 to (letter or historical article or comment or editorial or news or case reports)
20	18 not 19

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2 Embase (Ovid) search terms

1	Bone densitometry/ or dual energy X ray absorptiometry/
2	(densitometr* or BMD-test* or BMD-tool* or densimetr*).tw.
3	(bone adj4 mineral adj4 dens* adj4 test*).tw.
4	(bone adj4 mineral adj4 dens* adj4 tool*).tw.
5	Photon absorptiometry/
6	(absorptiometr* adj4 (dpx* or dual-energ* or dual-photon* or photon*)).tw.
7	(DXA* or DXA).tw.
8	or/1-7

9	exp Spine Fracture/
10	((spin* or vertebr* or neck or cervical or lumbar or sacral or thoracic or coccy* or cord or backbone* or back) adj4 (fracture* or compress*)).tw.
11	(compress* adj4 fracture*).tw.
12	(VCF or VFA* or IVA* or LVA* or DVA* or MXA*).tw.
13	((instant or lateral or densitometric or morphometric or dual-energ*) adj4 (vertebr* adj4 assess*)).tw.
14	(physician* adj4 viewer*).dv,tw.
15	or/9-14
16	8 and 15
17	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
18	16 not 17
19	nonhuman/ not human/
20	18 not 19
21	(letter or editorial).pt.
22	20 not 21
23	limit 22 to english language

Cochrane Library (Wiley) search terms

#1	MeSH descriptor: [Densitometry] explode all trees
#2	((densitometr* or BMD-test* or BMD-tool* or densimetr*)):ti,ab,kw
#3	((bone near/4 mineral near/4 dens* near/4 test*)):ti,ab,kw
#4	((bone near/4 mineral near/4 dens* near/4 tool*)):ti,ab,kw
#5	((absorptiometr* near/4 (dpx* or dual-energ* or dual-photon* or photon*))):ti,ab,kw
#6	((DXA* or DXA)):ti,ab,kw
#7	{or #1-#6}
#8	MeSH descriptor: [Spinal Fractures] this term only
#9	(((spin* or vertebr* or neck or cervical or lumbar or sacral or thoracic or coccy* or cord or backbone* or back) near/4 (fracture* or compress*))):ti,ab,kw
#10	((compress* near/4 fracture*)):ti,ab,kw
#11	((VCF or VFA* or IVA* or LVA* or DVA* or MXA*)):ti,ab,kw

#12	(((instant or lateral or densitometric or morphometric or dual NEXT energ*) near/4 (vertebr* near/4 assess*))):ti,ab,kw
#13	((physician* near/4 viewer*)):ti,ab,kw
#14	{or #8-#13}
#15	#7 and #14
#16	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#17	#15 not #16
#18	conference:pt
#19	#17 not #18

Epistemonikos search terms

1	title:((title:((densitometr* OR BMD AND test* OR BMD AND tool* OR densimetr*)) OR abstract:((densitometr* OR BMD AND test* OR BMD AND tool* OR densimetr*))) OR (title:((bone AND mineral AND dens* AND test*)) OR abstract:((bone AND mineral AND dens* AND test*))) OR (title:((bone AND mineral AND dens* AND tool*)) OR abstract:((bone AND mineral AND dens* AND tool*))) OR (title:((absorptiometr* AND (dpx* OR dual AND energ* OR dual AND photon* OR photon*))) OR abstract:((absorptiometr* AND (dpx* OR dual AND energ* OR dual AND photon* OR photon*)))) OR (title:((DXA* OR DXA)) OR abstract:((DXA* OR DXA)))
2	(title:(((spin* OR vertebr* OR neck OR cervical OR lumbar OR sacral OR thoracic OR coccy* OR cord OR backbone* OR back) AND (fracture* OR compress*))) OR abstract:(((spin* OR vertebr* OR neck OR cervical OR lumbar OR sacral OR thoracic OR coccy* OR cord OR backbone* OR back) AND (fracture* OR compress*)))) OR (title:((compress* AND fracture*)) OR abstract:((compress* AND fracture*))) OR (title:((VCF OR VFA* OR IVA* OR LVA* OR DVA* OR MXA*)) OR abstract:((VCF OR VFA* OR IVA* OR LVA* OR DVA* OR MXA*))) OR (title:(((instant OR lateral OR densitometric OR morphometric OR dual AND energ*) AND (vertebr* AND assess*))) OR abstract:(((instant OR lateral OR densitometric OR morphometric OR dual AND energ*) AND (vertebr* AND assess*)))) OR (title:((physician* AND viewer*)) OR abstract:((physician* AND viewer*))))
3	1 and 2

B.2 Health economic search literature search strategy

Health economic evidence was identified by conducting searches using terms for a population at risk of fragility fracture and for vertebral fracture assessment. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics.

Table 10: Database parameters, filters and limits applied for population at risk of fragility fracture

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 August 2025	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 22 August 2025	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 22 August 2025	English language

Medline (Ovid) search terms

1	exp Osteoporosis/
2	(osteopor* or osteo-por* or osteop?eni* or osteo-p?eni*).tw,kf.
3	((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 bone* adj4 (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit*)).tw.
4	((abnormal* or secondary or early or prematur*) adj4 bone* adj4 (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)).tw.
5	((low* or reduc* or decreas* or los*) adj4 bone* adj4 (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)).tw.
6	((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 BMD).tw.
7	((low* or los* or reduc* or decreas* or abnormal* or secondary) adj4 BMD).tw.
8	(bone* adj4 (deteriorat* or weak* or fragil* or decalc* or brittle* or atroph*)).tw.
9	((trabecula* or cancellous) adj4 (loss* or thin* or reduc* or decreas* or deteriorat* or low* or abnormal*)).tw.
10	((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 skeletal adj4 (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit* or decalc* or atroph*)).tw.
11	((abnormal* or secondary or early or prematur*) adj4 skeletal* adj4 (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit* or atroph*)).tw.
12	((low* or reduc* or decreas* or los*) adj4 skeletal adj4 (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)).tw.
13	Bone Diseases, Metabolic/
14	Osteoporotic Fractures/
15	(fragil* adj4 (fracture or fractures)).tw.
16	((low-impact* or low-energy or low-trauma* or insufficien*) adj4 fracture*).tw.
17	((risk* or frequen* or inciden* or suscept* or suspect* or predict* or prevent* or stop*) adj4 fracture*).tw.
18	((recurrent or recurring or repeat* or history or chronic or previous or prior or habitual) adj4 fracture*).tw.
19	refracture*.tw.
21	or/1-19
22	Economics/

23	Value of Life/
24	exp "Costs and Cost Analysis"/
25	exp Economics, Hospital/
26	exp Economics, Medical/
27	Economics, Nursing/
28	Economics, Pharmaceutical/
29	exp "Fees and Charges"/
30	exp Budgets/
31	budget*.ti,ab.
32	cost*.ti.
33	(economic* or pharmaco?economic*).ti.
34	(price* or pricing*).ti,ab.
35	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36	(financ* or fee or fees).ti,ab.
37	(value adj2 (money or monetary)).ti,ab.
38	or/22-37
39	21 and 38
40	limit 39 to ed=20140101-20250822

Embase (Ovid) search terms

1	exp osteoporosis/
2	exp Osteopenia/
3	(osteopor* or osteo-por* or osteop?eni* or osteo-p?eni*).tw,kf.
4	((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 bone* adj4 (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit*)).tw.
5	((abnormal* or secondary or early or prematur*) adj4 bone* adj4 (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)).tw.
6	((low* or reduc* or decreas* or los*) adj4 bone* adj4 (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)).tw.

7	((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 BMD).tw.
8	((low* or los* or reduc* or decreas* or abnormal* or secondary) adj4 BMD).tw.
9	(bone* adj4 (deteriorat* or weak* or fragil* or decalc* or brittle* or atroph*)).tw.
10	((trabecula* or cancellous) adj4 (loss* or thin* or reduc* or decreas* or deteriorat* or low* or abnormal*)).tw.
11	((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 skeletal* adj4 (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit* or decalc* or atroph*)).tw.
12	((abnormal* or secondary or early or prematur*) adj4 skeletal* adj4 (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit* or atroph*)).tw.
13	((low* or reduc* or decreas* or los*) adj4 skeletal* adj4 (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)).tw.
14	metabolic bone disease/ or exp bone demineralization/
15	fragility fracture/
16	(fragil* adj4 (fracture or fractures)).tw.
17	((low-impact* or low-energy or low-trauma* or insufficien*) adj4 fracture*).tw.
18	((risk* or frequen* or inciden* or suscept* or suspect* or predict* or prevent* or stop*) adj4 fracture*).tw.
19	((recurrent or recurring or repeat* or history or chronic or previous or prior or habitual) adj4 fracture*).tw.
20	refracture*.tw.
21	or/1-20
22	health economics/
23	exp economic evaluation/
24	exp health care cost/
25	exp fee/
26	budget/
27	funding/
28	budget*.ti,ab.
29	cost*.ti.
30	(economic* or pharmaco?economic*).ti.

31	(price* or pricing*).ti,ab.
32	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
33	(financ* or fee or fees).ti,ab.
34	(value adj2 (money or monetary)).ti,ab.
35	or/22-34
36	21 and 35
37	Limit 36 to dd=20140101-20250822
38	Limit 36 to dc=20140101-20250822
39	37 or 38

1

2 NHS EED and HTA (CRD) search terms

1	MeSH DESCRIPTOR osteoporosis EXPLODE ALL TREES
2	(((osteopor* or osteo-por* or osteopeni* or osteopaeni* or osteo-peni* or osteopaeni*)))
3	(((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 bone* adj4 (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit*)))
4	(((abnormal* or secondary or early or prematur*) adj4 bone* adj4 (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)))
5	(((low* or reduc* or decreas* or los*) adj4 bone* adj4 (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)))
6	(((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 BMD))
7	(((low* or los* or reduc* or decreas* or abnormal* or secondary) adj4 BMD))
8	((bone* adj4 (deteriorat* or weak* or fragil* or decalc* or brittle* or atroph*)))
9	(((trabecula* or cancellous) adj4 (loss* or thin* or reduc* or decreas* or deteriorat* or low* or abnormal*)))
10	((((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) adj4 skeletal adj4 (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit* or decalc* or atroph*))))

11	((((abnormal* or secondary or early or prematur*) adj4 skeletal* adj4 (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit* or atroph*))))
12	((((low* or reduc* or decreas* or los*) adj4 skeletal adj4 (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*))))
13	MeSH DESCRIPTOR Bone Diseases, Metabolic
14	MeSH DESCRIPTOR osteoporotic fractures
15	((fragil* adj4 (fracture or fractures)))
16	(((low-impact* or low-energy or low-trauma* or insufficien*) adj4 fracture*))
17	(((risk* or frequen* or inciden* or suscept* or suspect* or predict* or prevent* or stop*) adj4 fracture*))
18	(((recurrent or recurring or repeat* or history or chronic or previous or prior or habitual) adj4 fracture*))
19	(refracture*)
20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

1

2 INAHTA search terms

1	("Osteoporosis"[mhe])
2	(((osteopor* or osteopeni* or osteopaeni*))[Title] OR ((osteopor* or osteopeni* or osteopaeni*))[abs])
3	(((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) AND bone* AND (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit*)))[Title] OR (((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) AND bone* AND (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit*)))[abs]
4	(((abnormal* or secondary or early or prematur*) AND bone* AND (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)))[Title] OR (((abnormal* or secondary or early or prematur*) AND bone* AND (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)))[abs]
5	(((low* or reduc* or decreas* or los*) AND bone* AND (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*))) OR (((low* or reduc* or decreas* or los*) AND bone* AND (mass or architectur* or

	microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)))
6	(((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) AND BMD))[Title] OR (((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) AND BMD))[abs]
7	((low* or los* or reduc* or decreas* or abnormal* or secondary) AND BMD))[Title] OR (((low* or los* or reduc* or decreas* or abnormal* or secondary) AND BMD))[abs]
8	((bone* AND (deteriorat* or weak* or fragil* or decalc* or brittle* or atroph*)))[Title] OR ((bone* AND (deteriorat* or weak* or fragil* or decalc* or brittle* or atroph*)))[abs]
9	(((trabecula* or cancellous) AND (loss* or thin* or reduc* or decreas* or deteriorat* or low* or abnormal*)))[Title] OR (((trabecula* or cancellous) AND (loss* or thin* or reduc* or decreas* or deteriorat* or low* or abnormal*)))[abs]
10	(((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) AND skeletal AND (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit* or decalc* or atroph*)))[Title] OR (((age-relat* or agerelat* or perimenopaus* or peri-menopaus* or postmenopaus* or post-menopaus* or menopaus* or pathologic*) AND skeletal AND (los* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or demineral* or strength* or quality or quantit* or decalc* or atroph*)))[abs]
11	(((abnormal* or secondary or early or prematur*) AND skeletal* AND (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit* or atroph*)))[Title] OR (((abnormal* or secondary or early or prematur*) AND skeletal* AND (los* or reduc* or mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit* or atroph*)))[abs]
12	(((low* or reduc* or decreas* or los*) AND skeletal AND (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)))[Title] OR (((low* or reduc* or decreas* or los*) AND skeletal AND (mass or architectur* or microarchitectur* or micro-architectur* or dens* or mineral* or content or strength* or quality or quantit*)))[abs]
13	"Bone Diseases, Metabolic"[mh]
14	"Osteoporotic Fractures"[mh]
15	(fragil* AND (fracture or fractures))

16	((low-impact* or low-energy or low-trauma* or insufficien*) AND fracture*)
17	((risk* or frequen* or inciden* or suscept* or suspect* or predict* or prevent* or stop*) AND fracture*)
18	((recurrent or recurring or repeat* or history or chronic or previous or prior or habitual) AND fracture*)
19	refracture*
20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

Table 11: Database parameters, filters and limits applied for vertebral fracture assessment

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1946 – 22 August 2025	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1974 – 22 August 2025	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 22 August 2025	English language

Medline (Ovid) search terms

1	exp Densitometry/

2	(densitometr* or BMD-test* or BMD-tool* or densimetr*).tw.
3	(bone adj4 mineral adj4 dens* adj4 test*).tw.
4	(bone adj4 mineral adj4 dens* adj4 tool*).tw.
5	(absorptiometr* adj4 (dpx* or dual-energ* or dual-photon* or photon*)).tw.
6	(DXA* or DXA).tw.
7	or/1-6
8	Spinal Fractures/
9	((spin* or vertebr* or neck or cervical or lumbar or sacral or thoracic or coccy* or cord or backbone* or back) adj4 (fracture* or compress*)).tw.
10	(compress* adj4 fracture*).tw.
11	(VCF or VFA* or IVA* or LVA* or DVA* or MXA*).tw.
12	((instant or lateral or densitometric or morphometric or dual-energ*) adj4 (vertebr* adj4 assess*)).tw.
13	(physician* adj4 viewer*).tw.
14	or/8-13
15	7 and 14
16	VFRAC*.tw,kf.
17	(vertebr* adj4 fracture* adj4 screen* adj4 aid*).tw,kf.
18	(vertebr* adj4 fracture* adj4 screen* adj4 tool*).tw,kf.
19	(vertebr* adj4 fracture* adj4 screen* adj4 questionnaire*).tw,kf.
20	(vertebr* adj4 fracture* adj4 decision* adj4 aid*).tw,kf.
21	(vertebr* adj4 fracture* adj4 decision* adj4 tool*).tw,kf.
22	(vertebr* adj4 fracture* adj4 decision* adj4 questionnaire*).tw,kf.
23	(vertebr* adj4 fracture* adj4 assessment* adj4 aid*).tw,kf.
24	(vertebr* adj4 fracture* adj4 assessment* adj4 tool*).tw,kf.
25	(vertebr* adj4 fracture* adj4 assessment* adj4 questionnaire*).tw,kf.
26	(vertebr* adj4 fracture* adj4 clinical* adj4 aid*).tw,kf.
27	(vertebr* adj4 fracture* adj4 clinical* adj4 tool*).tw,kf.
28	(vertebr* adj4 fracture* adj4 clinical* adj4 questionnaire*).tw,kf.
29	(vertebr* adj4 fracture* adj4 checklist*).tw,kf.
30	(spin* adj4 fracture* adj4 screen* adj4 aid*).tw,kf.
31	(spin* adj4 fracture* adj4 screen* adj4 tool*).tw,kf.

32	(spin* adj4 fracture* adj4 screen* adj4 questionnaire*).tw,kf.
33	(spin* adj4 fracture* adj4 decision* adj4 aid*).tw,kf.
34	(spin* adj4 fracture* adj4 decision* adj4 tool*).tw,kf.
35	(spin* adj4 fracture* adj4 decision* adj4 questionnaire*).tw,kf.
36	(spin* adj4 fracture* adj4 assessment* adj4 aid*).tw,kf.
37	(spin* adj4 fracture* adj4 assessment* adj4 tool*).tw,kf.
38	(spin* adj4 fracture* adj4 assessment* adj4 questionnaire*).tw,kf.
39	(spin* adj4 fracture* adj4 clinical* adj4 aid*).tw,kf.
40	(spin* adj4 fracture* adj4 clinical* adj4 tool*).tw,kf.
41	(spin* adj4 fracture* adj4 clinical* adj4 questionnaire*).tw,kf.
42	(spin* adj4 fracture* adj4 checklist*).tw,kf.
43	(back adj4 pain adj4 screen* adj4 aid*).tw,kf.
44	(back adj4 pain adj4 screen* adj4 tool*).tw,kf.
45	(back adj4 pain adj4 screen* adj4 questionnaire*).tw,kf.
46	(back adj4 pain adj4 decision* adj4 aid*).tw,kf.
47	(back adj4 pain adj4 decision* adj4 tool*).tw,kf.
48	(back adj4 pain adj4 decision* adj4 questionnaire*).tw,kf.
49	(back adj4 pain adj4 assessment* adj4 aid*).tw,kf.
50	(back adj4 pain adj4 assessment* adj4 tool*).tw,kf.
51	(back adj4 pain adj4 assessment* adj4 questionnaire*).tw,kf.
52	(back adj4 pain adj4 clinical* adj4 aid*).tw,kf.
53	(back adj4 pain adj4 clinical* adj4 tool*).tw,kf.
54	(back adj4 pain adj4 clinical* adj4 questionnaire*).tw,kf.
55	(back adj4 pain adj4 checklist*).tw,kf.
56	(ISRCTN18000119 or ISRCTN12150779 or ISRCTN42028479 or ISRCTN16550671).tw,kf.
57	or/16-56
58	15 or 57
59	Economics/
60	Value of life/
61	exp "Costs and Cost Analysis"/
62	exp Economics, Hospital/

63	exp Economics, Medical/
64	Economics, Nursing/
65	Economics, Pharmaceutical/
66	exp "Fees and Charges"/
67	exp Budgets/
68	budget*.ti,ab.
69	cost*.ti.
70	(economic* or pharmaco?economic*).ti.
71	(price* or pricing*).ti,ab.
72	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
73	(financ* or fee or fees).ti,ab.
74	(value adj2 (money or monetary)).ti,ab.
75	or/59-74
76	58 and 75
77	animals/ not humans/
78	76 not 77
79	limit 78 to english language
80	limit 79 to (letter or historical article or comment or editorial or news or case reports)
81	79 not 80

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2 Embase (Ovid) search terms

1	Bone densitometry/ or dual energy X ray absorptiometry/
2	(densitometr* or BMD-test* or BMD-tool* or densimetr*).tw.
3	(bone adj4 mineral adj4 dens* adj4 test*).tw.
4	(bone adj4 mineral adj4 dens* adj4 tool*).tw.
5	(absorptiometr* adj4 (dpx* or dual-energ* or dual-photon* or photon*)).tw.
6	(DXA* or DXA).tw.
7	or/1-6
8	exp Spine Fracture/
9	((spin* or vertebr* or neck or cervical or lumbar or sacral or thoracic or coccy* or cord or backbone* or back) adj4 (fracture* or compress*)).tw.

10	(compress* adj4 fracture*).tw.
11	(VCF or VFA* or IVA* or LVA* or DVA* or MXA*).tw.
12	((instant or lateral or densitometric or morphometric or dual-energ*) adj4 (vertebr* adj4 assess*)).tw.
13	(physician* adj4 viewer*).tw.
14	or/8-13
15	7 and 14
16	VFRAC*.tw,kf.
17	(vertebr* adj4 fracture* adj4 screen* adj4 aid*).tw,kf.
18	(vertebr* adj4 fracture* adj4 screen* adj4 tool*).tw,kf.
19	(vertebr* adj4 fracture* adj4 screen* adj4 questionnaire*).tw,kf.
20	(vertebr* adj4 fracture* adj4 decision* adj4 aid*).tw,kf.
21	(vertebr* adj4 fracture* adj4 decision* adj4 tool*).tw,kf.
22	(vertebr* adj4 fracture* adj4 decision* adj4 questionnaire*).tw,kf.
23	(vertebr* adj4 fracture* adj4 assessment* adj4 aid*).tw,kf.
24	(vertebr* adj4 fracture* adj4 assessment* adj4 tool*).tw,kf.
25	(vertebr* adj4 fracture* adj4 assessment* adj4 questionnaire*).tw,kf.
26	(vertebr* adj4 fracture* adj4 clinical* adj4 aid*).tw,kf.
27	(vertebr* adj4 fracture* adj4 clinical* adj4 tool*).tw,kf.
28	(vertebr* adj4 fracture* adj4 clinical* adj4 questionnaire*).tw,kf.
29	(vertebr* adj4 fracture* adj4 checklist*).tw,kf.
30	(spin* adj4 fracture* adj4 screen* adj4 aid*).tw,kf.
31	(spin* adj4 fracture* adj4 screen* adj4 tool*).tw,kf.
32	(spin* adj4 fracture* adj4 screen* adj4 questionnaire*).tw,kf.
33	(spin* adj4 fracture* adj4 decision* adj4 aid*).tw,kf.
34	(spin* adj4 fracture* adj4 decision* adj4 tool*).tw,kf.
35	(spin* adj4 fracture* adj4 decision* adj4 questionnaire*).tw,kf.
36	(spin* adj4 fracture* adj4 assessment* adj4 aid*).tw,kf.
37	(spin* adj4 fracture* adj4 assessment* adj4 tool*).tw,kf.
38	(spin* adj4 fracture* adj4 assessment* adj4 questionnaire*).tw,kf.
39	(spin* adj4 fracture* adj4 clinical* adj4 aid*).tw,kf.
40	(spin* adj4 fracture* adj4 clinical* adj4 tool*).tw,kf.

41	(spin* adj4 fracture* adj4 clinical* adj4 questionnaire*).tw,kf.
42	(spin* adj4 fracture* adj4 checklist*).tw,kf.
43	(back adj4 pain adj4 screen* adj4 aid*).tw,kf.
44	(back adj4 pain adj4 screen* adj4 tool*).tw,kf.
45	(back adj4 pain adj4 screen* adj4 questionnaire*).tw,kf.
46	(back adj4 pain adj4 decision* adj4 aid*).tw,kf.
47	(back adj4 pain adj4 decision* adj4 tool*).tw,kf.
48	(back adj4 pain adj4 decision* adj4 questionnaire*).tw,kf.
49	(back adj4 pain adj4 assessment* adj4 aid*).tw,kf.
50	(back adj4 pain adj4 assessment* adj4 tool*).tw,kf.
51	(back adj4 pain adj4 assessment* adj4 questionnaire*).tw,kf.
52	(back adj4 pain adj4 clinical* adj4 aid*).tw,kf.
53	(back adj4 pain adj4 clinical* adj4 tool*).tw,kf.
54	(back adj4 pain adj4 clinical* adj4 questionnaire*).tw,kf.
55	(back adj4 pain adj4 checklist*).tw,kf.
56	(ISRCTN18000119 or ISRCTN12150779 or ISRCTN42028479 or ISRCTN16550671).tw,kf.
57	or/16-56
58	15 or 57
59	health economics/
60	exp economic evaluation/
61	exp health care cost/
62	exp fee/
63	budget/
64	funding/
65	budget*.ti,ab.
66	cost*.ti.
67	(economic* or pharmaco?economic*).ti.
68	(price* or pricing*).ti,ab.
69	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
70	(financ* or fee or fees).ti,ab.

71	(value adj2 (money or monetary)).ti,ab.
72	or/59-71
73	58 and 72
74	nonhuman/ not human/
75	73 not 74
76	limit 75 to english language
77	clinical trial.pt.
78	76 not 77
79	(letter or editorial).pt.
80	78 not 79
81	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
82	80 not 81

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2 NHS EED and HTA (CRD) search terms

1	MeSH DESCRIPTOR densitometry EXPLODE ALL TREES
2	((densitometr* or BMD-test* or BMD-tool* or densimetr*))
3	((bone adj4 mineral adj4 dens* adj4 test*))
4	((bone adj4 mineral adj4 dens* adj4 tool*))
5	((absorptiometr* adj4 (dpx* or dual-energ* or dual-photon* or photon*)))
6	((DXA* or DXA))
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	MeSH DESCRIPTOR Spinal Fractures
9	(((spin* or vertebr* or neck or cervical or lumbar or sacral or thoracic or coccy* or cord or backbone* or back) adj4 (fracture* or compress*)))
10	((compress* adj4 fracture*))
11	((VCF or VFA* or IVA* or LVA* or DVA* or MXA*))
12	(((instant or lateral or densitometric or morphometric or dual-energ*) adj4 (vertebr* adj4 assess*)))
13	((physician* adj4 viewer*))
14	#8 OR #9 OR #10 OR #11 OR #12 OR #13
15	#7 AND #14
16	(VFRAC*)

17	((vertebr* adj4 fracture* adj4 screen* adj4 aid*))
18	((vertebr* adj4 fracture* adj4 screen* adj4 tool*))
19	((vertebr* adj4 fracture* adj4 screen* adj4 questionnaire*))
20	((vertebr* adj4 fracture* adj4 decision* adj4 aid*))
21	((vertebr* adj4 fracture* adj4 decision* adj4 tool*))
22	((vertebr* adj4 fracture* adj4 decision* adj4 questionnaire*))
23	((vertebr* adj4 fracture* adj4 assessment* adj4 aid*))
24	((vertebr* adj4 fracture* adj4 assessment* adj4 tool*))
25	((vertebr* adj4 fracture* adj4 assessment* adj4 questionnaire*))
26	((vertebr* adj4 fracture* adj4 clinical* adj4 aid*))
27	((vertebr* adj4 fracture* adj4 clinical* adj4 tool*))
28	((vertebr* adj4 fracture* adj4 clinical* adj4 questionnaire*))
29	((vertebr* adj4 fracture* adj4 checklist*))
30	((spin* adj4 fracture* adj4 screen* adj4 aid*))
31	((spin* adj4 fracture* adj4 screen* adj4 tool*))
32	((spin* adj4 fracture* adj4 screen* adj4 questionnaire*))
33	((spin* adj4 fracture* adj4 decision* adj4 aid*))
34	((vertebr* adj4 fracture* adj4 assessment* adj4 tool*))
35	((spin* adj4 fracture* adj4 decision* adj4 questionnaire*))
36	((spin* adj4 fracture* adj4 assessment* adj4 aid*))
37	((spin* adj4 fracture* adj4 assessment* adj4 tool*))
38	((spin* adj4 fracture* adj4 assessment* adj4 questionnaire*))
39	((spin* adj4 fracture* adj4 clinical* adj4 aid*))
40	((spin* adj4 fracture* adj4 clinical* adj4 tool*))
41	((spin* adj4 fracture* adj4 clinical* adj4 questionnaire*))
42	((spin* adj4 fracture* adj4 checklist*))
43	((back adj4 pain adj4 screen* adj4 aid*))
44	((back adj4 pain adj4 screen* adj4 tool*))
45	((back adj4 pain adj4 screen* adj4 questionnaire*))
46	((back adj4 pain adj4 decision* adj4 aid*))
47	((back adj4 pain adj4 decision* adj4 tool*))
48	((back adj4 pain adj4 decision* adj4 questionnaire*))

49	((back adj4 pain adj4 assessment* adj4 aid*))
50	((back adj4 pain adj4 assessment* adj4 tool*))
51	((back adj4 pain adj4 assessment* adj4 questionnaire*))
52	((back adj4 pain adj4 clinical* adj4 aid*))
53	((back adj4 pain adj4 clinical* adj4 tool*))
54	((back adj4 pain adj4 clinical* adj4 questionnaire*))
55	((back adj4 pain adj4 checklist*))
56	((ISRCTN18000119 or ISRCTN12150779 or ISRCTN42028479 or ISRCTN16550671))
57	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56
58	#15 OR #57

INAHTA search terms

1	"Densitometry"[mhe]
2	((densitometr* or BMD-test* or BMD-tool* or densimetr*))
3	((bone and mineral and dens* and test*))
4	((bone and mineral and dens* and tool*))
5	((absorptiometr* and (dpx* or dual-energ* or dual-photon* or photon*)))
6	((DXA* or DXA))
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	"Spinal Fractures"[mh]
9	((spin* or vertebr* or neck or cervical or lumbar or sacral or thoracic or coccy* or cord or backbone* or back) and (fracture* or compress*))
10	(compress* and fracture*)
11	(VCF or VFA* or IVA* or LVA* or DVA* or MXA*)
12	((instant or lateral or densitometric or morphometric or dual-energ*) and (vertebr* and assess*))
13	(physician* and viewer*)
14	#8 OR #9 OR #10 OR #11 OR #12 OR #13
15	#7 AND #14
16	VFRAC*

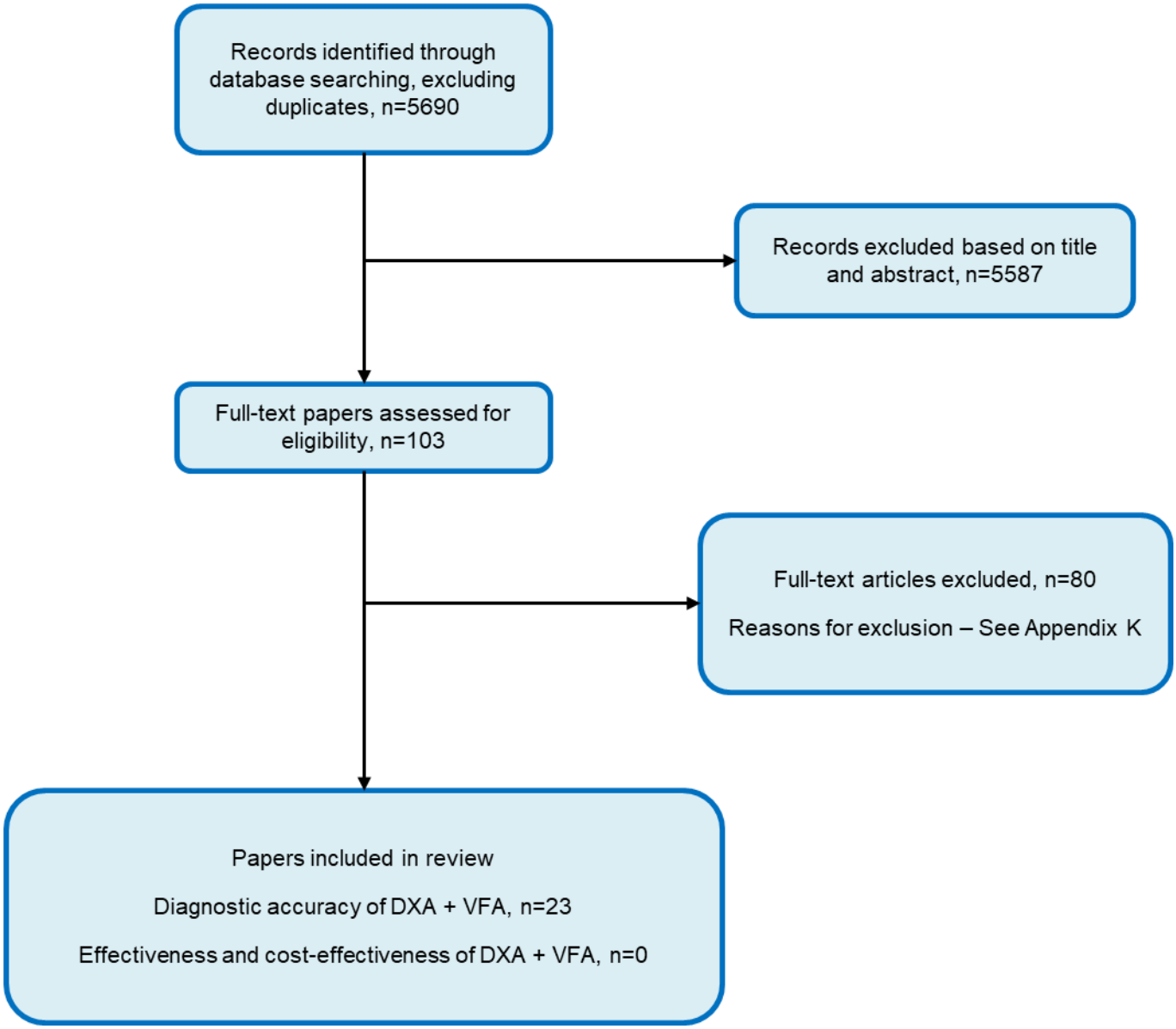
17	(vertebr* and fracture* and screen* and aid*)
18	(vertebr* and fracture* and screen* and tool*)
19	(vertebr* and fracture* and screen* and questionnaire*)
20	(vertebr* and fracture* and decision* and aid*)
21	(vertebr* and fracture* and decision* and tool*)
22	(vertebr* and fracture* and decision* and questionnaire*)
23	(vertebr* and fracture* and assessment* and aid*)
24	(vertebr* and fracture* and assessment* and tool*)
25	(vertebr* and fracture* and assessment* and questionnaire*)
26	(vertebr* and fracture* and clinical* and aid*)
27	(vertebr* and fracture* and clinical* and tool*)
28	(vertebr* and fracture* and clinical* and questionnaire*)
29	(vertebr* and fracture* and checklist*)
30	(spin* and fracture* and screen* and aid*)
31	(spin* and fracture* and screen* and tool*)
32	(spin* and fracture* and screen* and questionnaire*)
33	(spin* and fracture* and decision* and aid*)
34	(spin* and fracture* and decision* and tool*)
35	(spin* and fracture* and decision* and questionnaire*)
36	(spin* and fracture* and assessment* and aid*)
37	(spin* and fracture* and assessment* and tool*)
38	(spin* and fracture* and assessment* and questionnaire*)
39	(spin* and fracture* and clinical* and aid*)
40	(spin* and fracture* and clinical* and tool*)
41	(spin* and fracture* and clinical* and questionnaire*)
42	(spin* and fracture* and checklist*)
43	(back and pain and screen* and aid*)
44	(back and pain and screen* and tool*)
45	(back and pain and screen* and questionnaire*)
46	(back and pain and decision* and aid*)
47	(back and pain and decision* and tool*)
48	(back and pain and decision* and questionnaire*)

49	(back and pain and assessment* and aid*)
50	(back and pain and assessment* and tool*)
51	(back and pain and assessment* and questionnaire*)
52	(back and pain and clinical* and aid*)
53	(back and pain and clinical* and tool*)
54	(back and pain and clinical* and questionnaire*)
55	(back and pain and checklist*)
56	(ISRCTN18000119 or ISRCTN12150779 or ISRCTN42028479 or ISRCTN16550671)
57	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56
58	#15 OR #57

1

Appendix C Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for diagnostic accuracy and effectiveness of DXA-based VFA scan



Appendix D Diagnostic evidence

D.1 What is the diagnostic accuracy of DXA-based VFA scan or imaging), for identifying vertebral fractures?

Bazzocchi, 2012

Bibliographic Reference	Bazzocchi, Alberto; Spinnato, Paolo; Fuzzi, Federica; Diano, Danila; Morselli-Labate, Antonio M; Sassi, Claudia; Salizzoni, Eugenio; Battista, Giuseppe; Guglielmi, Giuseppe; Vertebral fracture assessment by new dual-energy X-ray absorptiometry.; Bone; 2012; vol. 50 (no. 4); 836-41

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** People with clinically suspected or diagnosed osteoporosis, chronic corticosteroid treatments or having follow-up after organ transplantations **Recruitment:** 68 consecutive patients who met indications for morphometric evaluation of the spine
Number of patients and fractures	Recruited: n=68; Excluded: n=0 Total, n=68 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 814/884 (92%)
Patient characteristics	**Age (mean):** 58.1 years (SD 9.6) **Gender-M/F:** 38/30 **Ethnicity:** NR

	Setting: NR (likely outpatient) **Country:** Italy **Inclusion criteria:** Clinically suspected or diagnosed osteoporosis, chronic corticosteroid treatments, follow-up after organ transplantations (for example, heart, liver) **Exclusion criteria:** History of previous oncologic disease, and presence of internal or external devices potentially overlapping the spine on lateral imaging view
Definition of vertebral fracture	Visual semi-quantitative-Genant method then quantitative morphometry if suspected vertebral fracture
Densitometric, radiographic or CT hardware used	DXA with VFA: GE Lunar iDXA Radiography: Apollo Genius HF-A
Index test(s) and reference standard	**Index test** DXA with dual-energy VFA. Lateral spine images were obtained with densitometric technique by an expert technologist. All scans were performed in standard manner following the manufacturer recommendations. VF diagnosed using Genant and then quantitative morphometric X-ray absorptiometry (using semi-automatic standard 6-point method) if suspected VF. Three physicians involved in study read anonymized radiographs and VFA scans with at least 1 week between evaluation of images of the same patients. Fourth physician supervised all reading sessions and collected results. In event of disagreement between VSQ and morphometric X-ray absorptiometry, latter classification preferred. **Reference standard** Lateral spine images were obtained with radiographic techniques (on the same day as the DXA scan) by an expert technologist. All scans were performed in standard manner following the recommendations suggested by the UCSF — Osteoporosis Research Group. VF defined using VSQ (Genant) method and then morphometric radiography (using manually-positioned 6 points) in case of suspected VF. Assessment of radiographs as above.

	Vertebrae range scanned for VFA: T4-L4 **Time between index and reference test:** Same day scan, anonymous analysis within 7 days			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	28	13	41
	Index test -	12	761	773
	Total	40	774	814
	Grade 1+, per-vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	8	3	11
	Index test -	7	796	804
	Total	15	799	814
	Grade 2+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	19	4	23
	Index test -	7	38	45

	Total	26	42	68
Statistical measures	**Per-vertebra analysis (n=814, n=40 VF≥Grade 1)** Sensitivity: 70.0% (95%CI 54.6-81.9) Specificity: 98.3% (95%CI 97.1-99.0) PPV: 68.0% (95%CI 52.8-80.2) NPV: 98.4% (95%CI 97.3-99.1) PLR: 41.2% (95%CI 23.2-73.0) NLR: 0.3% (95%CI 0.2-0.5) AUC: 0.842 (SE 0.044) Prevalence: 4.9% Note: Calculated, except for AUC, using reported number of VFs on conventional radiography and reported sensitivity/specificity. AUC outcome is as reported. **Per-vertebra analysis (n=814, n=15 VF≥Grade 2)** Sensitivity: 53.8% (95%CI 30.5-75.6) Specificity: 99.6% (95%CI 98.9-99.9) PPV: 71.6% (95%CI 42.7-89.5) NPV: 99.1% (95%CI 98.2-99.6) PLR: 134.5% (95%CI 40.9-442.3) NLR: 0.5% (95%CI 0.3-0.8) AUC: 0.767 (SE 0.062)			

	Prevalence: 1.8% Note: Calculated, except for AUC, using reported number of VFs on conventional radiography and reported sensitivity/specificity. AUC outcome is as reported. **Per-person analysis (n=68, n=26 with VF≥Grade 1)** Sensitivity: 73.1% (95%CI 53.9-86.3) Specificity: 90.5% (95%CI 78.0-96.2) PPV: 82.6% (95% CI 62.9-93.0) NPV: 84.5% (95%CI 71.2-92.3) PLR: 7.7% (95%CI 2.9-20.1) NLR: 0.3% (95%CI 0.2-0.6) AUC: 0.818 (SE 0.058) Prevalence: 38.2% Note: Calculated, except for AUC, using reported number of VFs on conventional radiography and reported sensitivity/specificity. AUC outcome is as reported.
Source of funding	Not reported
Limitations	Risk of bias: Moderate (unclear what position VFA scan obtained in) Indirectness: Directly applicable

Binkley, 2005

Bibliographic Reference	Binkley, Neil; Krueger, D; Gangnon, R; Genant, H K; Drezner, M K; Lateral vertebral assessment: a valuable technique to detect clinically significant vertebral fractures.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2005; vol. 16 (no. 12); 1513-8

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Postmenopausal women receiving osteoporosis treatment or having clinical bone mass measurements **Recruitment:** Invited by research study coordinator or densitometry technologist to participate in study
Number of patients and fractures	Recruited: n=80; Excluded: n= 1 (non-evaluable DXA) Total, n=79 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 834/1027 (81%)
Patient characteristics	**Age (mean):** 72.8 years (SD 4.5), range 61-84 years **Gender:** 100% women **Ethnicity:** NR **Setting:** Outpatient **Country:** USA **Inclusion criteria:** receiving osteoporosis treatment or having clinical bone mass measurements **Exclusion criteria:** NR

Definition of vertebral fracture	Visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: GE Lunar Prodigy Radiography: unclear, reports using digital imaging system immediately following VFA			
Index test(s) and reference standard	**Index test** Lateral decubitus DXA with dual-energy VFA independently evaluated by 2 non-radiologist physicians to mutually agree consensus interpretation. Non-evaluable vertebrae excluded from study and remaining images evaluated for VF using VSQ (Genant) method. **Reference standard** Lateral thoracolumbar conventional spinal radiograph obtained in routine clinical manner, analysed by expert skeletal radiologist using digital imaging system. VSQ (Genant) method used to classify VF. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** DXA with VFA and conventional radiograph obtained at same visit			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	28	30	58
	Index test -	12	764	776
	Total	40	794	834
	Grade 2+, per-vertebra analysis	**Reference standard +**	**Reference standard –**	**Total**

		X-ray	X-ray	
	Index test +	17	1	18
	Index test -	1	815	816
	Total	18	816	834
Statistical measures	**Per-vertebra analysis (n=834, n=40 with VF Grade≥1)** Sensitivity: 70.0% (95%CI 54.6-81.9) Specificity: 96.2% (95%CI 94.7-97.3) PPV: 48.3% (95%CI 35.9-60.8) NPV: 98.5% (95%CI 97.3-99.1) PLR: 18.5% (95%CI 12.4-27.8) NLR: 0.3% (95%CI 0.2-0.5) AUC: NR Prevalence: 4.8% Note: Calculated from raw data reported in study, excludes unreadable vertebrae. **Per-vertebra analysis (n=834, n=18 with VF Grade≥2)** Sensitivity: 94.4% (95%CI 74.2-99.0) Specificity: 99.9% (95%CI 99.3-100.0) PPV: 94.4% (95%CI 74.2-99.0)			

	NPV: 99.9% (95%CI 99.31-100.0) PLR: 770.7% (95%CI 108.3-5482.2) NLR: 0.1% (95%CI 0.0-0.4) AUC: NR Prevalence: 2.2% Note: Calculated from raw data reported in study, assuming that vertebrae classified as VF Grade 1 on either conventional radiography or DXA with VFA are normal. Excludes unreadable vertebrae.
Source of funding	Supported by grant from GE Medical Systems Lunar
Limitations	Risk of bias: High (Unclear whether consecutive or random recruitment; only one assessor of radiographs; unclear whether VFA interpreters blinded to results from other test; unclear position of scan) Indirectness: Directly applicable

Chapurlat, 2006

Bibliographic Reference	Chapurlat, R D; Duboeuf, F; Marion-Audibert, H O; Kalpakcioglu, B; Mitlak, B H; Delmas, P D; Effectiveness of instant vertebral assessment to detect prevalent vertebral fracture.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2006; vol. 17 (no. 8); 1189-95

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Postmenopausal women undergoing BMD measurement in absorptiometry center located in a university hospital

	Recruitment: Women attending hospital for screening absorptiometry or radiographic evaluation for VF
Number of patients and fractures	Recruited: n=85; Excluded: n=0 Total, n=85 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: NR
Patient characteristics	**Age (mean):** 71 years **Gender:** Female **Ethnicity:** NR **Setting:** Hospital setting (36 recruited from ambulatory and 49 from inpatient admissions) **Country:** Türkiye **Inclusion criteria:** postmenopausal women undergoing BMD measurement **Exclusion criteria:** NR
Definition of vertebral fracture	Visual (qualitative) then visual semi-quantitative-Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Delphi Radiography: Not reported, obtained with inpatients in hospital radiology department or with outpatients in radiology clinic

Index test(s) and reference standard	**Index test** DXA with single-energy 20s VFA scan in lateral position. VF were assessed using VSQ (Genant) method to define VF by 2 rheumatologists with osteoporosis expertise. **Reference standard** Conventional spinal radiography using qualitative then VSQ (Genant) method to classify VF by same 2 rheumatologists. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** Unclear, not reported			
2x2 table	**Grade 1+, per-person analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	30	11	41
	Index test -	13	31	44
	Total	43	42	85
Statistical measures	**Per-person analysis (n=85 participants, n=43 with VF Grade≥1)** Sensitivity: 69.0% (95%CI 54.1-80.8) Specificity: 74.0% (95%CI 59.1-84.8) PPV: 73.1% (95%CI 57.9-84.3) NPV: 70.0% (95%CI 55.4-81.4)			

	PLR: 2.7% (95%CI 1.5-4.6) NLR: 0.4% (95%CI 0.3-0.7) AUC: NR Prevalence: 50.6% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity. Per-vertebra analysis was not extracted because insufficient data was reported to allow calculation of raw data.
Source of funding	NR
Limitations	Risk of bias: Moderate (Unclear whether interpreters blinded to results of other test; unclear when index and reference tests conducted) Indirectness: Directly applicable

Damiano, 2006

Bibliographic Reference	Damiano, Joel; Kolta, Sami; Porcher, Raphael; Tournoux, Caroline; Dougados, Maxime; Roux, Christian; Diagnosis of vertebral fractures by vertebral fracture assessment.; Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry; 2006; vol. 9 (no. 1); 66-71

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Postmenopausal women with indication of spine radiography in rheumatology department

	Recruitment: Participants gave oral consent to have VFA at same time as DXA scan.
Number of patients and fractures	Recruited: n=136; Excluded: n=3 Total, n=133 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 1654/1904 (86.9%) using both methods
Patient characteristics	**Age (mean):** 69.1 years (SD 10), range 37-96 years **Gender:** 100% women **Ethnicity:** NR **Setting:** Outpatient **Country:** France **Inclusion criteria:** Indication for spine X-ray (for example, height loss, risk factor for postmenopausal osteoporosis and back pain, long-term corticosteroid therapy) **Exclusion criteria:** NR
Definition of vertebral fracture	Visual semi-quantitative-Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Delphi W Radiography: not reported
Index test(s) and reference standard	**Index test** Right lateral for lateral view and supine for anteroposterior view DXA with single-energy VFA, 3 days after conventional radiography, evaluated by 2 rheumatologists, one of which was more experienced than other. Each investigator read

	radiographs and VFA scans of same patient at least 1-mo apart. Evaluation of diagnostic value conducted using interpretations of more experienced investigator according to VSQ (Genant) method. **Reference standard** Lateral thoracolumbar conventional spinal radiograph, centred on T7 and L3, evaluated by same 2 rheumatologists using VSQ (Genant) method. **Vertebrae range scanned for VFA:** T4-L5 **Time between index and reference test:** DXA with VFA scan within 3 days of conventional radiography			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	120	25	145
	Index test -	25	1484	1509
	Total	145	1509	1654
	Grade 2+, per-vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	82	11	93
	Index test -	17	1544	1561
	Total	99	1555	1654
	Grade 1+, per-person analysis	**Reference standard +**	**Reference standard –**	**Total**

		X-ray	X-ray	
	Index test +	48	8	56
	Index test -	3	39	42
	Total	51	47	98
Statistical measures	**Per-vertebra analysis (n=1654, n=145 VF with Grade≥1)** Sensitivity: 82.8% (95%CI 75.8-88.04) Specificity: 98.3% (95%CI 97.6-98.9) PPV: 82.8% (95%CI 75.8-88.0) NPV: 98.3% (95%CI 97.6-98.9) PLR: 50.0% (95%CI 33.6-74.2) NLR: 0.2% (95%CI 0.1-0.3) AUC: NR Prevalence: 8.77% Note: Calculated from raw data reported in study, excluding unreadable vertebrae on either test. **Per-vertebra analysis (n=1654, n=99 VF with Grade≥2)** Sensitivity: 82.8% (95%CI 74.2-89.0) Specificity: 99.3% (95%CI 98.7-99.6) PPV: 88.2% (95%CI 80.0-93.3)			

	NPV: 98.9% (95%CI 98.3-99.3) PLR: 117.1% (95%CI 64.5-212.4) NLR: 0.2% (95%CI 0.1-0.3) AUC: NR Prevalence: 6.0% Note: Calculated from raw data reported in study, excluding unreadable vertebrae on either test and assuming that vertebrae evaluated as Grade 1 on either conventional radiography or DXA with VFA are normal. **Per-person analysis (n=133, n=61 with VF Grade≥1)** Sensitivity: 94.1% (95%CI 84.1-98.0) Specificity: 83.0% (95%CI 69.9-91.1) PPV: 85.7% (95%CI 74.3-92.6) NPV: 92.9% (95%CI 81.0-97.5) PLR: 5.5% (95%CI 2.9-10.4) NLR: 0.1% (95%CI 0.0-0.2) AUC: NR Prevalence: 52% Note: Calculated from raw data reported in study, excluding participants in which no diagnosis was possible (participant with one or more unreadable vertebrae with no fracture seen on legible vertebrae).
Source of funding	Not reported

Limitations	Risk of bias: High (Unclear selection of participants; 11% of vertebrae excluded for per-vertebra analysis and 26% of participants for per-person analysis) Indirectness: Directly applicable

Characteristics

Study-level characteristics

Characteristic	Study (N = 136)
Osteoporotic Sample size	n = 65; % = 48
Osteopenic Sample size	n = 46; % = 34
Normal BMD Sample size	n = 24; % = 18
Scoliosis Grade 1 Sample size	n = 56; % = 41
Scoliosis Grade 2 Sample size	n = 136; % = 10
Scoliosis Grade 3	n = 14; % = 1

Characteristic	Study (N = 136)
Sample size	
No scoliosis Sample size	n = 48; % = 65

Deleskog, 2016

Bibliographic Reference	Deleskog, L; Laursen, N O; Nielsen, B R; Schwarz, P; Vertebral fracture assessment by DXA is inferior to X-ray in clinical severe osteoporosis.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2016; vol. 27 (no. 7); 2317-2326

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Patients referred to the outpatient clinic of Research Centre for Ageing and Osteoporosis, Department of Endocrinology PE, Rigshospitalet, Copenhagen, Denmark **Recruitment:** Medical records of patients who were referred for teriparatide treatment at outpatient clinic from 01/2007 to 05/2015 were screened for those who had both conventional radiography and DXA with VFA within 6-mo before start of drug treatment. Of 207 potentially relevant records: 142 were excluded due to lack of index test, reference test, or both; 5 were excluded for other reasons. Of remaining 60 records, 21 were excluded due to missing either thoracic or lumbar images on X-ray.

Number of patients and fractures	Recruited: n=39; Excluded: n=4 (did not meet criteria for severe osteoporosis based on radiologically diagnosed VF and BMD criteria) Total, n=35 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 368/455 (81%)
Patient characteristics	**Age (mean):** 67.5 years **Gender (M/F):** 5/30 **Ethnicity:** NR **Setting:** Outpatient **Country:** Denmark **Inclusion criteria:** Severe osteoporosis, referred to outpatient clinic for teriparatide treatment; had DXA with VFA in addition to thoracolumbar radiography within 6 months before the start of teriparatide treatment **Exclusion criteria:** Not meeting criteria for severe osteoporosis; suffering from cancer or calcium metabolic diseases other than osteoporosis
Definition of vertebral fracture	Visual semi-quantitative-Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Discovery A QDR Series Radiography: not reported, obtained directly from workstations in radiology wards
Index test(s) and reference standard	**Index test** DXA with single-energy VFA scan in lateral decubitus position. VF defined by using VSQ (Genant) method, assessed by endocrinologist with expertise in osteoporosis and calcium metabolic diseases. Assessor could manually change placement

	of points conducted by technician but did not reassess vertebral interpretations, which were set to certain by technician. Endocrinologist conducted assessments independently of radiologist. **<u>Reference standard</u>** Antero-posterior and lateral thoracolumbar conventional spinal radiographs. VF defined by using VSQ (Genant) method by experienced radiologist, who reviewed all vertebral interpretations conducted by technician. Radiologist conducted assessments independently of endocrinologist. **Vertebrae range scanned for VFA:** T5-L5 **Time between index and reference test:** Conventional radiography and DXA with VFAs conducted 1-week apart with order randomised in each case			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	108	30	138
	Index test -	35	195	230
	Total	143	225	368
	Grade 2+, per-vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	78	22	100
	Index test -	30	238	268
	Total	108	260	368

Statistical measures	**Per-vertebra analysis (n=368 vertebrae, n=143 with VF Grade≥1)** Sensitivity: 75.5% (95%CI 67.9-81.8) Specificity: 86.7% (95%CI 81.6-90.5) PPV: 78.3% (95%CI 70.7-84.3) NPV: 84.8% (95%CI 79.6-88.9) PLR: 5.7% (95%CI 4.0-8.0) NLR: 0.3% (95%CI 0.2-0.4) AUC: NR Prevalence: 38.9% Note: Calculated using reported raw data, excluding unreadable vertebrae on either test. **Per-vertebra analysis (n=368 vertebrae, n=108 with VF Grade≥2)** Sensitivity: 72.2% (95%CI 63.1 -79.8) Specificity: 91.5% (95%CI 87.5-94.3) PPV: 78.0% (95%CI 68.9 -85.0) NPV: 88.8% (95%CI 84.5- 92.0) PLR: 8.5% (95%CI 5.6-13.0) NLR: 0.3% (95%CI 0.2-0.4) AUC: NR Prevalence: 29.3%

	Note: Calculated using reported raw data, assuming that grade 1 VF on either DXA with VFA or conventional radiography are normal and excluding unreadable vertebrae on either test.
Source of funding	Eli Lilly, Denmark, and The Lundbeck Foundation
Limitations	Risk of bias: High (Study only includes people with severe osteoporosis; 19% evaluable vertebrae were excluded as unreadable; only one assessor of radiographs) Indirectness: Directly applicable

Diacinti, 2012A

Bibliographic Reference	Diacinti, Daniele; Del Fiacco, Romano; Pisani, Daniela; Todde, Federico; Cattaruzza, Maria Sofia; Diacinti, Davide; Arima, Serena; Romagnoli, Elisabetta; Pepe, Jessica; Cipriani, Cristiana; Minisola, Salvatore; Diagnostic performance of vertebral fracture assessment by the lunar iDXA scanner compared to conventional radiography.; Calcified tissue international; 2012; vol. 91 (no. 5); 335-42

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Referrals to Mineral Metabolism Centre for diagnosis of osteoporosis and patients from study of HIV-related osteoporosis **Recruitment:** Post or perimenopausal women and men consecutively referred to centre. Number of participants from each source not reported.
Number of patients and fractures	Recruited: n=350; Excluded: n=0 Total, n=350

	Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 4476/4550 (98.4%) on DXA with VFA
Patient characteristics	**Age** (mean): 60.6 years (SD 11.6), range 28-85 **Gender (M/F):** 81/269 **Ethnicity:** NR **Setting:** Outpatient **Country:** Italy **Inclusion criteria:** peri- and post- menopausal women and men referred by GP for osteoporosis diagnosis or participating in HIV-related osteoporosis study **Exclusion criteria:** NR
Definition of vertebral fracture	Visual - algorithm-based qualitative (ABQ) method then visual semi-quantitative - Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: GE Lunar iDXA Radiography: Apollo DRF
Index test(s) and reference standard	**Index test** Lateral thoracolumbar spine DXA with dual-energy VFA in left lateral decubitus position. enCORE software v13.5 performed vertebral morphometry and images reviewed (and amended according to Hurxthal criteria) by physician specialist in bone diseases (5-7 years VFA experience). Physician classified vertebral fracture using ABQ method excluding other causes of vertebral deformities. Fifty randomly selected spinal DXA images checked twice by physician, blinded to previous analysis, with interval of no more than 30 days between readings. **Reference standard**

	Left lateral and anteroposterior thoracolumbar conventional spinal radiograph centered at T7 and L3, evaluated by experienced skeletal radiologist using ABQ method to discriminate non-fracture deformities and then VSQ (Genant) method to classify true VFs. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** DXA with VFA conducted at same time as conventional radiographs			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	228	4	232
	Index test -	3	4315	4318
	Total	231	4319	4550
	Grade 1+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	122	3	125
	Index test -	4	221	225
	Total	126	224	350
Statistical measures	**Per-vertebra analysis (n=4550, n=231 with VF Grade≥1)** Sensitivity: 98.7% (95%CI 96.2-99.5) Specificity: 99.9% (95%CI 99.8-100.0)			

	PPV: 98.3% (95%CI 95.7-99.4) NPV: 99.9% (95%CI 99.8-100.0) PLR: 1096.0% (95%CI 405.9-2962.0) NLR: 0.01% (95%CI 0.0-0.04) AUC: NR Prevalence: 5.1% Note: Calculated from the reported number of VF according to reference standard and reported sensitivity/specificity, with unreadable vertebrae on either test treated as normal. **Per-person analysis (n=350, n=126 with VF Grade≥1)** Sensitivity: 96.8% (95%CI 92.1-98.8) Specificity: 98.7% (95%CI 96.1-99.5) PPV: 97.6% (95%CI 93.2-99.2) NPV: 98.2% (95%CI 95.5-99.3) PLR: 72.3% (95%CI 23.5-222.6) NLR: 0.03% (95%CI 0.01-0.08) AUC: NR Prevalence: 36% Note: Calculated from the reported number of people with VF according to reference standard and reported sensitivity/specificity. Number of people with unreadable vertebrae not reported.
Source of funding	Reports no conflict of interest

Limitations	Risk of bias: High (Sample includes osteoporotic adults with HIV, number not reported; Only one assessor of radiographs) Indirectness: Directly applicable

Diacinti, 2012B

Bibliographic Reference	Diacinti, D; Guglielmi, G; Pisani, D; Diacinti, D; Argiro, R; Serafini, C; Romagnoli, E; Minisola, S; Catalano, C; David, V; Vertebral morphometry by dual-energy X-ray absorptiometry (DXA) for osteoporotic vertebral fractures assessment (VFA).; La Radiologia medica; 2012; vol. 117 (no. 8); 1374-85

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Women referred for osteoporosis evaluation **Recruitment:** Postmenopausal women consecutively referred to mineral metabolism centre by GP for osteoporosis evaluation
Number of patients and fractures	Recruited: n=930; Excluded: n=0 Total, n=930 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 11,980/12,090 (99.1%)
Patient characteristics	**Age (mean):** 62.43 years, (SD 11.55), range 46-85 **Gender:** 100% women **Ethnicity:** NR

	Setting: Outpatient **Country:** Italy **Inclusion criteria:** Postmenopausal women referred to centre **Exclusion criteria:** NR			
Definition of vertebral fracture	Visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic QDR-4500A Radiography: Apollo DRF digital radiographic system			
Index test(s) and reference standard	**Index test** Supine lateral DXA with single-energy VFA using VSQ (Genant). Expert skeletal radiologist checked automatic vertebral height measurements and manually corrected if incorrect (Hurxthal criteria) with all vertebral deformities not due to fractures excluded (for example, artefacts, developmental abnormalities, Scheuermann's disease). Vertebral morphometry of 50 patients randomly selected and repeated twice by radiologist blinded to previous morphometric analysis. Reanalysis after approximately 30 days. **Reference standard** Anterior-posterior and left-lateral conventional spinal radiographs using digital radiographic system, centered at T7 and L3, evaluated by different experienced skeletal radiologist using VSQ (Genant) method. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** DXA with VFA at same time as conventional radiography			
2x2 table	**Grade 1+, per-person analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**

	Index test +	410	10	420
	Index test -	32	11,638	11,670
	Total	442	11,648	12,090
	Grade 1+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	246	0	246
	Index test -	5	679	684
	Total	251	679	930
Statistical measures	**Per-vertebra analysis (n=12,090, n=442 with VF Grade≥1)** Sensitivity: 92.8% (95%CI 90.0-94.8) Specificity: 99.9% (95%CI 99.8-100.0) PPV: 97.6% (95%CI 95.7-98.7) NPV: 99.7% (95%CI 99.6-99.8) PLR: 1080.5% (95%CI 581.2-2008.7) NLR: 0.07% (95%CI 0.05-0.10) AUC: NR Prevalence: 3.7% Note: Outcome measures calculated from raw diagnostic data reported in study, treating unreadable vertebrae as normal.			

	Per-person analysis (n=930, n=251 with VF Grade≥1) Sensitivity: 98.0% (95%CI 95.4-99.1) Specificity: 100.0% (95%CI 99.4-100.0) PPV: 100.0% (95%CI 98.5-100.0) NPV: 99.3% (95%CI 98.3-99.7) PLR: Not estimable NLR: 0.02% (95%CI 0.01-0.05) AUC: NR Prevalence: 27.0% Note: Outcome measures calculated from raw diagnostic data reported in study, treating participants with unreadable vertebrae as normal. Results reported in article and slightly different to those reported here.
Source of funding	Reports no conflict of interest
Limitations	Risk of bias: High (Only one assessor of radiographs) Indirectness: Directly applicable

Characteristics

Study-level characteristics

Characteristic	Study (N = 930)
Osteoporotic	n = 663; % = 71.3

Characteristic	Study (N = 930)
Sample size	
Osteopenic Sample size	n = 233; % = 25.1
Normal BMD Sample size	n = 33; % = 3.6

Domiciano, 2013

Bibliographic Reference	Domiciano, Diogo S; Figueiredo, Camille P; Lopes, Jaqueline B; Kuroishi, Marcia E; Takayama, Liliam; Caparbo, Valeria F; Fuller, Priscila; Menezes, Paulo F; Scazufca, Marcia; Bonfa, Eloisa; Pereira, Rosa M R; Vertebral fracture assessment by dual X-ray absorptiometry: a valid tool to detect vertebral fractures in community-dwelling older adults in a population-based survey.; Arthritis care & research; 2013; vol. 65 (no. 5); 809-15

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Participants in previous epidemiological project (SPAH study) in Sao Paulo, Brazil **Recruitment:** Participants in SPAH study agreed to participate in study, which was conducted 06/2005 to 06/2009

Number of patients and fractures	Recruited: n=429; Excluded: n=0 Total, n=429 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 5276/5577 (94.6%) on DXA with VFA
Patient characteristics	**Age (mean):** 73.02 years (SD 5.09) **Gender (M/F):** 170/259 **Ethnicity:** NR **Setting:** Outpatient **Country:** Brazil **Inclusion criteria:** participation in previous SPAH project, aged ≥65 years, lives in Butanta, Sao Paulo, Brazil. **Exclusion criteria:** NR
Definition of vertebral fracture	Visual semi-quantitative-Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Discovery Radiography: not reported, radiographs not digitized
Index test(s) and reference standard	**Index test** DXA with single-energy VFA in supine position performed by experienced technologist and evaluated by 2 experienced rheumatologists using VSQ (Genant) method. Consensus of image interpretation reached, and non-visible vertebrae excluded. Random sample of 60 VFA images independently evaluated by rheumatologists. **Reference standard**

	Lateral thoracolumbar conventional spinal radiographs using Hologic centered at T7 and L2, evaluated by 2 experienced skeletal radiologists using VSQ (Genant) method. Images not digitized. Random sample of 60 radiographs independently evaluated by these radiologists. **Vertebrae range scanned:** T4-L4 **Time between index and reference test:** DXA with VFA on same day as conventional radiography			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	167	47	214
	Index test -	61	4952	5013
	Total	228	4999	5227
	Grade 2+, per-vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	61	9	70
	Index test -	33	5124	5157
	Total	94	5133	5227
	Grade 1+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	103	22	125

	Index test -	23	281	304
	Total	126	303	429
	Grade 2+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	57	1	58
	Index test -	8	363	371
	Total	65	364	429
Statistical measures	**Per-vertebra analysis (n=5227, n=228 with VF Grade≥1)** Sensitivity: 73.2% (95%CI 67.1-78.6) Specificity: 99.1% (95%CI 98.8-99.3) PPV: 78.0% (95%CI 72.0-83.1) NPV: 98.8% (95%CI 98.4-99.1) PLR: 71.9% (95%CI 58.0-104.7) NLR: 0.3% (95%CI 0.2-0.3) AUC: NR Prevalence: 4.4% Note: Calculated from raw data reported in study, which excludes unreadable vertebrae. **Per-vertebra analysis (n=5227, n=94 with VF Grade≥2)**			

Sensitivity: 64.9% (95%CI 54.8-73.8)

Specificity: 99.8% (95%CI 99.7-99.9)

PPV: 87.1% (95%CI 77.3-93.1)

NPV: 99.4% (95%CI 99.1-99.5)

PLR: 370.1% (95%CI 189.5-722.9)

NLR: 0.4% (95%CI 0.3-0.5)

AUC: NR

Prevalence: 1.8%

Note: Calculated from raw data reported in study assuming that vertebrae classified as grade 1 by either DXA with VFA or by conventional radiography are normal. Study reports sensitivity/specificity, PPV and NPV excluding Grade 1 fracture cases but not clear how these were calculated given reported raw data.

Per-person analysis (n=429, n=126 with VF Grade≥1)

Sensitivity: 81.7% (95%CI 74.00-87.5)

Specificity: 92.7% (95%CI 89.2-95.1)

PPV: 82.3% (95%CI 74.7-88.0)

NPV: 92.4% (95%CI 88.9-94.9)

PLR: 11.2% (95%CI 7.4-16.9)

NLR: 0.2% (95%CI 0.1-0.3)

AUC: NR

Prevalence: 29.4%

	Note: Calculated from reported number of VF on conventional radiography and reported sensitivity/specificity. **Per-person analysis (n=429, n=65 with VF Grade≥2)** Sensitivity: 87.7% (95%CI 77.5-93.6) Specificity: 99.7% (95%CI 98.5-100.0) PPV: 98.3% (95%CI 90.9-99.7) NPV: 92.4% (95%CI 88.9-94.9) PLR: 319.0% (95%CI 45.0-2265.0) NLR: 0.12% (95%CI 0.06-0.24) AUC: NR Prevalence: 15.2% Note: Calculated from reported number of VF on conventional radiography and reported sensitivity/specificity.
Source of funding	Supported by FAPESP (grant 03/09313-0) and individual grants to authors
Limitations	Risk of bias: Moderate (Unclear if consecutive/random recruitment; for per-vertebra analysis 6% excluded due to unreadability on DXA with VFA) Indirectness: Partially applicable (community sample)

Ferrar, 2000

Bibliographic Reference	Ferrar, L; Jiang, G; Barrington, N A; Eastell, R; Identification of vertebral deformities in women: comparison of radiological assessment and quantitative morphometry using morphometric radiography and morphometric X-ray absorptiometry.; Journal of

bone and mineral research : the official journal of the American Society for Bone and Mineral Research; 2000; vol. 15 (no. 3); 575-85

Study details

Study type	Cross-sectional study Reference population (DXA with VFA and conventional radiograph conducted at same time) Prospective cohort study Osteoporotic population (>2-week gap between index and reference tests)
Study methodology	**Data source:** Women participating in prospective population-based BMD study in Sheffield, UK (reference population); women with evidence of osteoporotic vertebral fracture referred to the Metabolic Bone Clinic, Northern General Hospital, Sheffield, UK (osteoporotic population) **Recruitment:** Women in reference population participating in BMD study were originally randomly selected from 3 GP populations in Sheffield, UK (n=375). Women excluded if GP felt too ill or unable to provide informed consent. Uptake rate was 55% in original study. Total of 242 women attended FU BMD scans and spinal radiographs at 5 years; of these, 123 participants consented to have DXA with VFA . Women in osteoporotic population were referred to metabolic bone unit of Northern General Hospital Trust, Sheffield, UK, and those with. spinal radiographs available for assessment were included.
Number of patients and fractures	Recruited: Reference population, n=375; Excluded: n=133 (did not attend 5-yr FU appointment); n=119 (did not consent to DXA with VFA due to scoliosis, poor mobility, or unwillingness to undergo further exams in addition to those in original study) Osteoporotic population, n=83, Excluded, n=0

	Total: Reference population, n=123; Osteoporotic population, n=83 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: Reference population: 1381/1599 (86%); Osteoporotic population: 915/1064 (86%)
Patient characteristics	**Reference population** **Age (mean):** 66.6 years (SD 7.3), range 56-88 years **Gender:** 100% Female **Ethnicity:** NR **Setting:** Outpatient **Country:** UK **Inclusion criteria:** Female; registered at 1 of 3 GP practices in Sheffield, UK; attended 5-year FU appointment; consented to have DXA with VFA **Exclusion criteria:** GP assessed participant as too ill to participate in study; inability to provide informed consent **Osteoporotic population** **Age (mean):** 70 years (SD 9), range 49-87 years **Gender:** 100% Female **Ethnicity:** NR **Setting:** Outpatient **Country:** UK **Inclusion criteria:** Referred to the metabolic bone unit at the Northern General Hospital Trust, Sheffield, UK; qualitative radiological evidence of osteoporotic vertebral fracture; available spinal radiographs to assess

	Exclusion criteria: NR			
Definition of vertebral fracture	Visual - method unspecified then visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic QDR-4500A Radiography: not reported, obtained using standardized protocol			
Index test(s) and reference standard	**Index test** DXA with single- and dual-energy (high definition) VFA. VF defined using consensus reading of qualitative visual assessment (Melton method) by experienced radiologist and one of study authors. Atlas of radiological variants used as guide to assessment. Side-by-side analysis of single- and dual- energy scans was conducted with single-energy scans marked and dual-energy HD scan used as visual aid to point placement. All scans marked by one operator. **Reference standard** Conventional spinal radiography with VF defined using consensus reading of qualitative visual assessment (Melton method) by same experienced radiologist and study author, with all radiographs marked by same operator as for DXA with VFA. Severity of identified (consensus) VF then assessed by second radiologist using VSQ (Genant method). **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** For reference population, DXA with VFA and conventional radiography on same day; for osteoporotic population, majority had DXA with VFA and conventional radiography on same day and there was <5-mo gap between these for all participants. All radiographs marked by one operator using Melton method.			
2x2 table	**Grade 1+, per-vertebra analysis – Reference population**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	13	41	54

	Index test -	10	1317	1327
	Total	23	1358	1381
	Grade 2+, per-vertebra analysis – Osteoporotic population	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	250	31	281
	Index test -	55	580	635
	Total	305	611	916
Statistical measures	**<u>Reference population</u>** **Per-vertebra analysis (n=1381, n=23 with VF Grade≥1)** Sensitivity: 58.0% (95%CI 38.1-75.6) Specificity: 97.0% (95%CI 96.0-97.8) PPV: 24.7% (95%CI 15.1-37.6) NPV: 99.3% (95%CI 98.7-99.6) PLR: 19.3% (95%CI 12.2-30.7) NLR: 0.4% (95%CI 0.3-0.7) AUC: NR Prevalence: 1.7%			

	Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity, excluding unreadable vertebrae on DXA with VFA (3 VF missed by DXA with VFA as excluded due to unreadability). **<u>Osteoporotic population</u>** **Per-vertebra analysis (n=915, n=305 with VF Grade≥1)** Sensitivity: 82.0% (95%CI 77.3-85.9) Specificity: 95.0% (95%CI 93.0-96.5) PPV: 89.1% (95%CI 84.9-92.3) NPV: 91.3% (95%CI 88.9-93.3) PLR: 16.4% (95%CI 11.6-23.3) NLR: 0.19% (95%CI 0.15-0.24) AUC: NR Prevalence: 33.3% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity, excluding unreadable vertebrae on DXA with VFA (40 VF missed by DXA with VFA as excluded due to unreadability).
Source of funding	National Osteoporosis Society, UK, and by an Arthritis Research Campaign Program Grant
Limitations	Risk of bias: For osteoporotic population, Risk of bias is High due to no information about blinding of index text/reference standard tests; gap >2 weeks between index and reference test for some participants (number not reported); patient flow may have introduced bias due to exclusion of 14% unreadable vertebrae. For reference population, Risk of bias is High due to no information about blinding of index text/reference standard tests, community sample form GP practices.

	Indirectness: Directly applicable

Ferrar, 2003

Bibliographic Reference	Ferrar, L; Jiang, G; Eastell, R; Peel, N F A; Visual identification of vertebral fractures in osteoporosis using morphometric X-ray absorptiometry.; Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research; 2003; vol. 18 (no. 5); 933-8

Study details

Study type	Prospective cohort study Uses index and reference test results at both baseline and 1-year FU
Study methodology	**Data source:** Women referred with osteoporosis to the Metabolic Bone Clinic, Northern General Hospital, Sheffield, UK **Recruitment:** Women with osteoporosis (BMD T score < -2.5 and/or vertebral fractures) and willing to participate in the study
Number of patients and fractures	Recruited: n=70; Excluded: n=0 Total, n=70 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: NR
Patient characteristics	**Age (mean):** 67 years **Gender:** 100% female

	Ethnicity: NR **Setting:** Osteoporosis clinic **Country:** UK **Inclusion criteria:** postmenopausal women, BMD T score less than -2.5 and/or vertebral fractures **Exclusion criteria:** use of any medication or existence of any disease or condition influencing bone density; use of statins or diuretics; and history of neoplasia, mild stroke, deep vein thrombosis, or psychiatric illness
Definition of vertebral fracture	Visual - unspecified method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic QDR-4500A Radiography: not reported, obtained in Diagnostic Imaging Department using standardized protocol
Index test(s) and reference standard	**Index test** Postero-anterior and lateral DXA with single- and dual-energy (high definition) VFA scans conducted in the supine position. VFs diagnosed using both visual and quantitative morphometric X-ray absorptiometry. Three observers assessed VFA scans using visual assessment: observer A was skeletal radiologist; observer B was physician with osteoporosis expertise); observer C was expert in quantitative vertebral morphometry with no formal training in assessing spinal radiographs. Quantitative assessment of VF on WFA images was conducted by observer C only. **Reference standard** Antero-posterior and lateral thoracolumbar conventional spinal radiograph done at baseline. Lateral projections conducted at the follow-up. VFs diagnosed using visual assessment of radiographs. Two observers (A and B) conducted visual assessment of radiographs with observer A's assessment of spinal radiographs treated as reference standard. **Vertebrae range scanned for VFA:** T4-L4

	Time between index and reference test: Conventional radiography and DXA with VFA conducted at same appointment, both at baseline at 1-year FU. Assessments used both baseline and FU (when available) scans.			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	271	25	296
	Index test -	24	471	495
	Total	291	496	791
	Grade 2+, per-vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	153	13	166
	Index test -	8	617	625
	Total	161	630	791
Statistical measures	**Per-vertebra analysis (n=791 vertebra, n=295 with VF Grade≥1)** Sensitivity: 92.0% (95%CI 88.3-94.6) Specificity: 95.0% (95%CI 92.7-96.6) PPV: 91.6% (95%CI 87.9-94.3) NPV: 95.2% (95%CI 93.0-96.8) PLR: 18.40% (95%CI 12.52-27.04)			

	NLR: 0.08% (95%CI 0.06-0.12) AUC: NR Prevalence: 37.3% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity. These data are for Observer A only comparing their visual assessment of DXA with VFA to their visual assessment of conventional radiography. **Per-vertebra analysis (n=791 vertebra, n=161 with VF Grade≥2)** Sensitivity: 95.0 (95%CI 90.5-97.4) Specificity: 98.0% (95%CI 96.6-98.8) PPV: 92.4% (95%CI 87.3-95.5) NPV: 98.7% (95%CI 97.5-99.3) PLR: 47.5% (95%CI 27.5-82.5) NLR: 0.1% (95%CI 0.0-0.1) AUC: NR Prevalence: 20.4% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity. These data are for Observer A only comparing their visual assessment of DXA with VFA to their visual assessment of conventional radiography.
Source of funding	National Osteoporosis Society, UK

Limitations	Risk of bias: Moderate (Unclear whether index/reference test results were analyzed with knowledge of the other test; although 2 assessors of radiographs, only one assessor used to determine reference standard; 29% of sample did not have DXA with VFA at 1-year FU due to administrative error) Indirectness: Directly applicable

Ferrar, 2008

Bibliographic Reference	Ferrar, Lynne; Jiang, Guirong; Clowes, Jackie A; Peel, Nicola F; Eastell, Richard; Comparison of densitometric and radiographic vertebral fracture assessment using the algorithm-based qualitative (ABQ) method in postmenopausal women at low and high risk of fracture.; Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research; 2008; vol. 23 (no. 1); 103-11

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Postmenopausal women either at low-risk of osteoporotic fracture population via participation in OPUS study or at high risk of osteoporotic fracture population via metabolic bone centre. **Recruitment:** Women at low risk of osteoporotic fracture (age 55-79) were from random population-based sample participating in Sheffield, UK arm of Europe-wide OPUS study from 1999-2001. Women at several Sheffield GPs were asked to complete questionnaire and asked whether they would be interested in participating, with those not initially attending for scans invited for a second appointment. Women who did not attend either appointment were excluded from study. Response rates stratified by 5-year age groups were monitored and adjusted to achieve homogenous distribution across age groups. Women at high risk of osteoporotic fracture were recruited from postmenopausal women attending Metabolic bone Centre, Northern General Hospital, Sheffield, UK for assessment after low-trauma fracture. Women had (i) sustained low-trauma fracture (proximal femur, proximal humerus, or distal forearm), (ii) been diagnosed with prevalent VF, or (iii) been receiving

	prednisolone therapy≥5 mg daily for >3-months. Women with forearm or humeral fractures consecutively recruited from orthopaedic ward; those with hip fractures recruited from orthopaedic wards; those with VFs were recruited from new referrals to bone clinic. Women on prednisolone therapy recruited form outpatient clinics. For both populations, only women with both conventional radiography and DXA with VFA images were included in sample.
Number of patients and fractures	Recruited: Low risk population, n=459, High-risk population, n= 298; Excluded: n=0 Total: Low-risk population, n=459; High-risk population, n=298 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: NR
Patient characteristics	**Women at low risk of osteoporotic fracture** **Age (mean):** 68 years (SD 7), range 55-79 years **Gender:** 100% Female **Ethnicity:** NR **Setting:** Outpatient **Country:** UK **Inclusion criteria:** postmenopausal women **Exclusion criteria:** disorders that precluded valid QUS measurements, general inability to undergo the specified exams, and cognitive limitations that preclude filling out self-administered questionnaires and pregnant women **Women at high risk of osteoporotic fracture** **Age (mean):** 69.1 years (SD 7), range 55-80 years **Gender:** 100% Female **Ethnicity:** NR

	Setting: Outpatient **Country:** UK **Inclusion criteria:** postmenopausal women attending the Metabolic Bone Center, Sheffield, UK, having recently sustained low-trauma fracture (of the proximal femur, proximal humerus, or distal forearm), been diagnosed with prevalent VF, or had been receiving prednisolone **Exclusion criteria:** NR
Definition of vertebral fracture	Visual - algorithm-based qualitative (ABQ) method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic QDR-4500A Radiography: not reported, used standardized protocol
Index test(s) and reference standard	**Index test** DXA scan using single-energy VFA. A centerline scan of the thoraco-lumbar spine was first obtained (postero-anterior projection), followed by supine lateral projection. Lateral scans were acquired using the single-energy scan mode. Experienced radiologist assessed densitometric images using the Algorithm-based qualitative diagnosis (ABQ) method before assessment of spinal radiographs. **Reference standard** Conventional digitized (before ABQ assessment) spinal radiograph conducted in lateral decubitus position. Same experienced radiologist assessed conventional radiographs using the Algorithm-based qualitative diagnosis (ABQ) method. Spinal radiograph assessment occurred at least 3 weeks after VFA assessment, with radiographer blinded to VFA results. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** Conventional radiography conducted at same appointment after DXA with VFA

2x2 table	**Grade 1+, per-person analysis – Low risk population**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	37	11	48
	Index test -	15	396	411
	Total	52	407	459
	Grade 2+, per-person analysis – Low risk population	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	23	2	25
	Index test -	8	426	434
	Total	31	428	459
	Grade 1+, per-person analysis – High risk population	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	**72**	**7**	79
	Index test -	**14**	**205**	219
	Total	**86**	**212**	298

	Grade 2+, per-person analysis – High risk population	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	51	9	60
	Index test -	9	229	238
	Total	60	238	298
Statistical measures	**High-risk of osteoporotic fracture population** **Per-person analysis (n=298 participants, n=86 with VF Grade≥1)** Sensitivity: 84.3% (95%CI 75.2-90.5) Specificity: 96.8% (95%CI 93.5-98.5) PPV: 91.4% (95%CI 83.2-95.8) NPV: 93.8% (95%CI 89.8-96.3) PLR: 26.3% (95%CI 12.5-55.6) NLR: 0.2% (95%CI 0.1-0.3) AUC: NR Prevalence: 28.9% **Per-person analysis (n=298 participants, n=60 with VF Grade≥2)** Sensitivity: 85.7% (95%CI 74.7-92.4) Specificity: 96.4% (95%CI 93.2-98.1)			

	PPV: 85.7% (95%CI 74.7-92.4) NPV: 96.4% (95%CI 93.2-98.1) PLR: 23.8% (95%CI 12.2-46.3) NLR: 0.2% (95%CI 0.1-0.3) AUC: NR Prevalence: 20.1% Note: per-vertebra diagnostic accuracy outcomes also reported but insufficient information to calculate raw diagnostic data. Therefore, this data has not been extracted. **Low risk of osteoporotic fracture population** **Per-person analysis (n=459 participants, n=52 with VF Grade≥1)** Sensitivity: 71.2% (95%CI 57.8-81.7) Specificity: 97.4% (95%CI 95.4-98.6) PPV: 77.8% (95%CI 64.1-87.2) NPV: 96.4% (95%CI 94.1-97.8) PLR: 27.4% (95%CI 14.7-50.9) NLR: 0.3% (95%CI 0.2-0.5) AUC: NR Prevalence: 11.3% **Per-person analysis (n=459 participants, n=31 with VF Grade≥2)** Sensitivity: 74.4% (95%CI 57.0-86.4)

	Specificity: 99.5% (95%CI 98.3-99.9) PPV: 91.5% (95%CI 74.5-97.5) NPV: 98.2% (95%CI 96.4-99.1) PLR: 148.8% (95%CI 38.5-575.3) NLR: 0.3% (95%CI 0.1-0.5) AUC: NR Prevalence: 6.8% Note: per-vertebra diagnostic accuracy outcomes also reported but insufficient information to calculate raw diagnostic data. Therefore, this data has not been extracted.
Source of funding	Reports that one author (LF) funded by Medical Research Council, UK.
Limitations	**At high-risk of osteoporotic fracture population** Risk of bias: High (only one assessor of radiographs; High-risk of vertebral fracture population was not consecutive or random sample;) Indirectness: Directly applicable **At low-risk of osteoporotic fracture population** Risk of bias: High (only one assessor of radiographs) Indirectness: Directly applicable

Fuerst, 2009

Bibliographic Reference	Fuerst, T; Wu, C; Genant, H K; von Ingersleben, G; Chen, Y; Johnston, C; Econs, M J; Binkley, N; Vokes, T J; Crans, G; Mitlak, B H; Evaluation of vertebral fracture assessment by dual X-ray absorptiometry in a multicenter setting.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2009; vol. 20 (no. 7); 1199-205

Study details

Study type	Retrospective cohort study
Study methodology	**Data source:** Postmenopausal women with osteoporosis **Recruitment:** Radiographic data collected from three clinical sites that had conducted prior VFA examinations in patients with osteoporosis
Number of patients and fractures	Recruited: n=203; Excluded: n=0 Total, n=203 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 2270/2639 (86%)
Patient characteristics	**Age (mean):** 67.5 years (SD 9.6) **Gender:** 100% Female **Ethnicity:** NR **Setting:** Outpatient **Country:** USA **Inclusion criteria:** Postmenopausal woman; available DXA with VFA scan and conventional radiographs

	Exclusion criteria: NR			
Definition of vertebral fracture	Visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Delphi or GE Lunar Prodigy Radiography: not reported, obtained using standard radiographic film or digital x-ray equipment			
Index test(s) and reference standard	**Index test** DXA with single-energy (Hologic Delphi) or dual-energy (Lunar Prodigy) VFA. Lateral imaging of thoracolumbar spine. VF assessed using VSQ (Genant) method by consensus of three radiologists. 99 VFA scans were obtained using Hologic Delphi scanner and 104 by GE Lunar Prodigy scanner. VFA and radiographic images read blindly twice with interval of at least 2 weeks between them. **Reference standard** Lateral imaging of thoracolumbar conventional (film or electronic digital) spinal radiograph, assessed by same 3 radiologists using VSQ (Genant) method. Difference of interpretation resolved by consensus. VFA and radiographic images read twice with interval of at least 2 weeks between them. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** reports both tests obtained on same day or within a few days			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	76	22	98

	Index test -	33	2139	2172
	Total	109	2161	2270
	Grade 2+, per- vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	39	22	61
	Index test -	17	2192	2209
	Total	56	2214	2270
Statistical measures	**Per-vertebra analysis (n=2270, with n=109 VF Grade≥1)** Sensitivity: 70.0% (95%CI 60.8-77.8) Specificity: 99.0% (95%CI 98.5-99.3) PPV: 77.9% (95%CI 68.7-85.0) NPV: 98.5% (95%CI 97.9-98.9) PLR: 70.0% (95%CI 45.2-108.4) NLR: 0.3% (95%CI 0.2-0.4) AUC: NR Prevalence: 4.8% Note: Calculated using reported first consensus number of VF on conventional radiography and reported sensitivity/specificity for this.			

	Per-vertebra analysis (n=2270, with n=56 VF Grade≥2) Sensitivity: 70.0% (95%CI 57.0-80.4) Specificity: 99.0% (95%CI 98.5-99.3) PPV: 63.9% (95%CI 51.4-74.8) NPV: 99.2% (95%CI 98.8-99.5) PLR: 70.0% (95%CI 44.7-109.6) NLR: 0.3% (95%CI 0.2-0.5) AUC: NR Prevalence: 2.5% Note: Calculated using reported first consensus number of VF on conventional radiography and reported sensitivity/specificity for this.
Source of funding	Eli Lilly and Co.
Limitations	Risk of bias: High (unclear recruitment strategy; different machines used for VFA scans (Hologic Delphi, Lunar Prodigy); ~12% unreadable vertebrae) Indirectness: Directly applicable

Hospers, 2009

Bibliographic Reference	Hospers, I.C.; Van Der Laan, J.G.; Zeebregts, C.J.; Nieboer, P.; Wolffenbuttel, B.H.R.; Dierckx, R.A.; Kreeftenberg, H.G.; Jager, P.L.; Slart, R.H.J.A.; Vertebral fracture assessment in supine position: Comparison by using conventional semiquantitative radiography and visual radiography; Radiology; 2009; vol. 251 (no. 3); 822-828

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Medical records of patients suspected of having primary or secondary osteoporosis and referred for BMD testing at department of nuclear medicine, University of Groningen, Netherlands **Recruitment:** Retrospective study of patients>50 years-old referred from many departments/outpatient clinics for conventional radiography from 2006-2007.
Number of patients and fractures	Recruited: n=258; Excluded: n=8 (not able to lie supine during DXA with VFA) Total, n=250 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 3208/3250 (98.7%)
Patient characteristics	**Age (mean):** 62 years, range 25-89 years **Gender:** 60/190 **Ethnicity:** NR **Setting:** Outpatient **Country:** Netherlands **Inclusion criteria:** age>50 years-old, referred for BMD scan and conventional radiography,

	Exclusion criteria: patients with metal implant who were unable to lie supine; unreadable vertebrae due to obesity or overlapping organs			
Definition of vertebral fracture	Visual semi-quantitative- unspecified method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Discovery Radiography: Siemans MULTIX Swing			
Index test(s) and reference standard	**Index test** Lateral DXA with single-energy VFA in supine position, evaluated by 1 of 2 operators using Hologic QDR viewer software, manually adjusted if needed, and blinded to conventional radiography results. VF categorized using VSQ method. **Reference standard** Lateral thoracolumbar conventional spine radiography, evaluated by 1 experienced (20 years + experience) radiologist using VSQ method. Second reading by second radiologist in difficult cases. In addition, semi-quantitative radiography (MRX) conducted and evaluated by 2 operators. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** Conventional radiographs obtained within 1 week after DXA with VFA			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	135	24	159
	Index test -	26	2682	2708

	Total	161	2706	2867
Statistical measures	**Per-vertebra analysis (DXA with VFA compared to visual radiography as reference standard; n=2867, n=161 with VF Grade≥1)** Sensitivity: 83.6% (95%CI 77.1-88.5) Specificity: 99.1% (95%CI 98.7-99.4) PPV: 84.7% (95%CI 78.3-89.5) NPV: 99.0% (95%CI 98.6-99.3) PLR: 92.9% (95%CI 62.2-138.8) NLR: 0.2% (95%CI 0.1-0.2) AUC: NR Prevalence: 46.5% Note: Calculated from reported number of VF on visual interpretation of lateral radiographs and reported sensitivity and specificity. Data from DXA with VFA compared to morphometric radiography as reference standard has not been extracted.			
Source of funding	Report no financial relationship to disclose			
Limitations	Risk of bias: High (Excludes people living with obesity and people with overlapping organs; ~12% evaluable vertebrae were unreadable) Limitations: Directly applicable			

Lee, 2014

Bibliographic Reference	Lee, JH; Cho, SK; Han, M; Lee, S; Kim, JY; Ryu, JA; Choi, YY; Bae, Sung, YK; Validity and role of vertebral fracture assessment in detecting prevalent vertebral fracture in patients with rheumatoid arthritis; Joint Bone Spine; 2014; vol. 81(2)

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Women with Rheumatoid arthritis (RA) attending university hospital for periodic examination **Recruitment:** Women recruited between 04/2011 to 08/2011.
Number of patients and fractures	Recruited: n=169; Excluded: n=69 (recently checked for BMD or did not consent) Total, n=100 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 1130/1300 (87%)
Patient characteristics	**Age, mean (SD) years:** 61.2 (SD 8.2) **Gender:** 100% women **Ethnicity:** NR **Setting:** Outpatient **Country:** Italy **Inclusion criteria:** Women with RA who visited the university hospital for periodic examination between April 2011 and August 2011. Patients aged 50 years or older and who fulfilled the American College of Rheumatology (ACR) 1987 revised classification criteria **Exclusion criteria:** Individuals who were recently checked for BMD or not consented **Participants receiving steroids at baseline:** 57/100 (57%)

Definition of vertebral fracture	Quantitative morphometry (X-ray or radiographic, as appropriate) then visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Discovery W Radiography: not reported			
Index test(s) and reference standard	**Index test** Lateral spine DXA with single-energy VFA. VFA examination was performed using a bone densitometer with the patient in lateral decubitus position. For assessment of VFs, two experienced nuclear medicine physicians used qualitative morphometric X-ray absorptiometry to diagnose VF then VSQ (Genant) method to classify severity. Six parameters were calculated automatically by the DXA device. VFA interpretation was done independently by two nuclear medicine physicians. Vertebra considered fractured only when the two VFA readers interpreted it as fractured. However, consensus reading between two readers was not done for different interpretations. **Reference standard** Lateral imaging of the thoracolumbar spine by radiography. All radiographs were analysed by two experienced radiologists. Discrepancies between radiologists in the presence of fracture, fracture type and grade were resolved by consensus and these results were defined as the reference standard. By two radiologists, qualitative fracture evaluation using morphometric radiography was performed to decide whether the vertebral fracture was present or not and semiquantitative method was used to classify the severity of vertebral deformity as mild (grade 1), moderate (grade 2), or severe (grade 3). Vertebral levels that could not be adequately visualized were classified as “unreadable.” **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** same day or within 7 days			
2x2 table	**Grade 1+, per-person analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	35	11	46

	Index test -	12	42	54
	Total	47	53	100
Statistical measures	**Per-person analysis (n=100, n=47 with VF Grade≥1)** Sensitivity: 74.5 (95%CI 60.5-84.7) Specificity: 79.2% (95%CI 66.5-88.0) PPV: 76.1% (95%CI 62.1-86.1) NPV: 77.8% (95%CI 65.1-86.8) PLR: 3.6% (95%CI 2.1-6.2) NLR: 0.3% (95%CI 0.2-0.5) AUC: NR Prevalence of VF determined using radiography: 47% Note: Outcome measures calculated from raw diagnostic data reported in study.			
Source of funding	This study was supported by the research fund of Hanyang University (HY-2009-000-0000-0969).			
Limitations	Risk of bias: Moderate (Unclear whether assessors were blinded to results of other test) Limitations: Directly applicable			

Lin, 2017

Bibliographic Reference	Lin, Y-C; Huang, T-S; Wu, J S; Cheung, Y-C; Huang, Y-H; Sung, C-M; Juan, Y-H; Chen, F-P; Ni Mhuircheartaigh, J M; Are bilateral decubitus views necessary in assessing for vertebral compression fractures using DXA vertebral fracture

assessment?.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2017; vol. 28 (no. 8); 2377-2382

Study details

Study type	Retrospective cohort study Greater than 2-week gap between index and reference test for some participants
Study methodology	**Data source:** Postmenopausal women who received DXA scan for osteoporosis evaluation between 03/2013 and 06/2015 at Chang Gung Memorial Hospital, Taiwan **Recruitment:** Radiology records of women reviewed and those who had conventional lateral lumbar radiographs within 1-mo of DXA scan were identified.
Number of patients and fractures	Recruited: n=114; Excluded: n=0 Total, n=114 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 798/798 (100%)
Patient characteristics	**Age (mean):** NR **Gender:** 100% women **Ethnicity:** NR **Setting:** Outpatient **Country:** Taiwan **Inclusion criteria:** Postmenopausal women who had conventional spinal radiography within one month of DXA with VFA. **Exclusion criteria:** NR

Definition of vertebral fracture	Visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: GE Lunar iDXA Radiography: Toshiba KXO-50R			
Index test(s) and reference standard	**Index test** Left lateral decubitus DXA with dual-energy VFA conducted, followed by repeat right lateral decubitus VFA scan using VFA software employing VSQ (Genant) method for classification of VF (standard practice at study institution). Process of placing points was fully automated and not manually adjusted. **Reference standard** Lateral lumbar spine conventional radiography conducted covering T10-L5 using VSQ (Genant) method, evaluated by radiologist with 6-years' experience and blinded to VFA results. Cobb angles measured using posteroanterior absorptiometry image. **Vertebrae range scanned for VFA:** T8-L4 **Time between index and reference test:** Conventional radiography conducted within 1 month of DEX with VFA			
2x2 table	**Grade 1+, per-vertebra analysis – left and right lateral decubitus position**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	33	44	77
	Index test -	9	712	721
	Total	42	756	798

	Grade 1+, per-person analysis – left decubitus position	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	27	21	48
	Index test -	15	735	750
	Total	42	756	798
Statistical measures	**Per-vertebra analysis (n=798, n=42 with VF Grade≥1, combined scan using scans from both right and left lateral decubitus position)** Sensitivity: 78.6% (95%CI 64.1-88.3) Specificity: 94.2% (95%CI 92.3-95.7) PPV: 43.0% (95%CI 32.5-54.1) NPV: 98.8% (95%CI 97.6-99.3) PLR: 13.55% (95%CI 9.76-18.81) NLR: 0.23% (95%CI 0.13-0.41) AUC: NR Prevalence: 5.3% Note: Outcome measures calculated from reported total number of vertebrae, reported number of VFs according to conventional radiography and reported sensitivity/specificity. Study also reports outcomes for right lateral decubitus DXA with VFA compared to conventional radiography. This data has not been extracted. **Per-vertebra analysis (n=798, n=42 with VF Grade≥1, left lateral decubitus position)**			

	Sensitivity: 64.3% (95%CI 49.2-77.0) Specificity: 97.2% (95%CI 95.8-98.2) PPV: 56.1% (95%CI 42.1-69.1) NPV: 98.0% (95%CI 96.7-98.8) PLR: 23.0% (95%CI 14.3-37.0) NLR: 0.4% (95%CI 0.2-0.6) AUC: NR Prevalence: 5.3% Note: Outcome measures calculated from reported total number of vertebrae, reported number of VFs according to conventional radiography and reported sensitivity/specificity. Study also reports outcomes for right lateral decubitus DXA with VFA compared to conventional radiography. This data has not been extracted.
Source of funding	Reports no conflict of interest
Limitations	Risk of bias: High (May include some participants who had conventional radiography more than 2 weeks after DXA with VFA scan; position of VFA scan not reported; only one assessor of radiographs) Indirectness: Directly applicable

Malgo, 2017

Bibliographic Reference	Malgo, F; Hamdy, N A T; Ticheler, C H J M; Smit, F; Kroon, H M; Rabelink, T J; Dekkers, O M; Appelman-Dijkstra, N M; Value and potential limitations of vertebral fracture assessment (VFA) compared to conventional spine radiography: experience from a fracture liaison service (FLS) and a meta-analysis.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2017; vol. 28 (no. 10); 2955-2965

Study details

Study type	Retrospective cohort study Unclear when index and reference tests were conducted
Study methodology	**Data source:** Database of patients electronic medical records who were assessed for osteoporosis according to screening protocols used in Fracture Liaison Service (FLS), June 2012-2014 **Recruitment:** All patients attending FLS of Leiden University Medical Centre screened, diagnosed, and treated for osteoporosis when required.
Number of patients and fractures	Recruited: n=552; Excluded: n=0 Total: n=552 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: NR
Patient characteristics	**Age (mean):** 67.5 years (SD 10.1) **Gender (M/F):** 137/405 **Ethnicity:** NR **Setting:** Outpatient **Country:** Netherlands **Inclusion criteria:** electronic medical records of women aged≥50 years, sustained fracture between June 2012-2014, assessed for osteoporosis according to FLS screening protocols **Exclusion criteria:** NR

Definition of vertebral fracture	Visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic QDR-4500 Radiography: not reported, used standardized protocol			
Index test(s) and reference standard	**Index test** DXA with single-energy lateral VFA images of spine in supine position, performed by technician who adjusted points as needed. NHANES III reference values compatible with Dutch population used to calculate T-scores. VF assessed using Hologic QDR Physician Viewer software. VSQ (Genant≥grade 2) method used to categorize VF. **Reference standard** Anteroposterior (thoracic spine) and posteroanterior (lumbar spine), and lateral conventional spinal radiographs of thoracolumbar spine, centralized on T7 and L3. All routinely generated reports of conventional radiograph performed retrieved from Electronic Medical Records. One author assessed all radiographs for presence and grade of VF using VSQ (Genant) method. Both technician and author blinded to VFA findings. Disagreement between radiology report and evaluation by author resolved by experienced musculoskeletal radiologist, who also evaluated 20% random selected sample of remaining patients. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test: DXA with VFA:** unclear, study implies DXA with VFA conducted at same time as conventional radiography but not explicitly stated			
2x2 table	**Grade 2+, per-person analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	102	82	184

	Index test -	30	328	358
	Total	132	410	542
Statistical measures	**Per-person analysis (n=542, n=132 with VF Grade≥2)** Sensitivity: 77.3% (95%CI 69.4-83.6) Specificity: 80.0% (95%CI 75.9-83.6) PPV: 55.4% (95%CI 48.2-62.4) NPV: 91.6% (95%CI 88.3-94.1) PLR: 3.9% (95%CI 3.1-4.8) NLR: 0.3% (95%CI 0.2-0.4) AUC: NR Prevalence: 24.4% Note: Outcome measures calculated using reported raw data in study.			
Source of funding	Reports no conflict of interest			
Limitations	Risk of bias: High (Retrospective study so only includes people who had both DXA with VFA and conventional radiography; Unclear what interval, if any, between DXA with VFA scan and conventional radiography; not all conventional radiographs were interpreted by radiologist) Indirectness: Directly applicable			

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Osteoporosis Sample size	n = 163 ; % = 30
Osteopenia Sample size	n = 319 ; % = 59
Normal BMD Sample size	n = 60 ; % = 11
Vertebra Sample size	n = 25 ; % = 5
Hip Sample size	n = 50 ; % = 9
Proximal humerus Sample size	n = 58 ; % = 11
Ankle Sample size	n = 61 ; % = 11

Mazzaferro, 2006

Bibliographic Reference	Mazzaferro, Sandro; Diacinti, Daniele; Proietti, Emanuela; Barresi, Giusi; Baldinelli, Matteo; Pisani, Daniela; D'Erasmo, Emilio; Pugliese, Francesco; Morphometric X-ray absorptiometry in the assessment of vertebral fractures in renal transplant patients.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2006; vol. 21 (no. 2); 466-71

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Renal transplant patients **Recruitment:** Patients on standard triple or double immunosuppressive therapy recruited for study
Number of patients and fractures	Recruited: n=53; Excluded: n=0 Total, n=53 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 669/689 (97.1%) on DXA
Patient characteristics	**Age (mean):** 45.0 years (SD 12.0) **Gender (M/F):** 31/22 **Ethnicity:** NR **Setting:** Outpatient **Country:** Italy **Inclusion criteria:** renal transplant patient, on standard triple or double immunosuppressive therapy, asymptomatic for fractures, stable clinical condition **Exclusion criteria:** NR

	Participants receiving steroids at baseline: NR
Definition of vertebral fracture	Index test: Quantitative morphometric X-ray absorptiometry Reference test: Visual semi-quantitative-Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic QDR-4500A Radiography: not reported, used standardized protocol
Index test(s) and reference standard	**Index test** Two lateral DXA with VFA in supine position using single-energy and dual-energy HD scan modes. Quantitative morphometric X-ray absorptiometry (MXA) performed by trained operator on single-energy scans using semi-automatic analysis with DXA scanner software. Morphometric definition of VF used reference ranges obtained from healthy population of 300 premenopausal women and 100 young adult men. **Reference standard** Anteroposterior and left lateral thoracolumbar conventional spinal radiograph following standardized protocol, centered at T7 and L3, evaluated by experienced skeletal radiologist using VSQ (Genant) method. Posteroanterior lumbar spine scans and left hip acquired to measure BMD. MRX (morphometric radiography) also conducted on digitalized lateral spinal radiographs by physician skilled in diagnosing osteoporosis. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** DXA with VFA at same time as conventional radiography

	Grade 1+, per-vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	49	5	54

	Index test -	0	635	635
	Total	49	640	689
	Grade 1+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	17	0	17
	Index test -	0	36	36
	Total	17	36	53
Statistical measures	**Per-vertebra analysis (using morphometric X-ray absorptiometry (MXA) as index test) (n=689, n=49 with VF Grade≤1)** Sensitivity: 100.0% (95%CI 92.7-100.0) Specificity: 99.2% (95%CI 98.2-99.7) PPV: 90.7% (95%CI 80.1-96.0) NPV: 100.0% (95%CI 99.4-100.0) PLR: 128.0% (95%CI 53.5-306.5) NLR: not estimable AUC: NR Prevalence: 7.1% Note: Calculated from raw data reported in study.			

	Per-person analysis (using morphometric X-ray absorptiometry (MXA) as index test) (n=53, n=17 with VF Grade≤1) Sensitivity: 100.0% (95%CI 81.6-100.0) Specificity: 100.0% (95%CI 90.4-100.0) PPV: 100.0% (95%CI 81.6-100.0) NPV: 100.0% (95%CI 90.4-100.0) PLR: not estimable NLR: not estimable AUC: NR Prevalence: 32.1% Note: Calculated from raw data reported in study.
Source of funding	Reports no conflict of interest
Limitations	Risk of bias: High (Unclear recruitment strategy; different definitions of vertebral fracture used for index and reference tests; only one assessor of radiographs) Indirectness: Directly applicable

Rea, 2000B

Bibliographic Reference	Rea, J A; Li, J; Blake, G M; Steiger, P; Genant, H K; Fogelman, I; Visual assessment of vertebral deformity by X-ray absorptiometry: a highly predictive method to exclude vertebral deformity.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2000; vol. 11 (no. 8); 660-8

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Guy's Hospital Osteoporosis Unit for osteoporosis screening, and the Metabolic Bone Clinic (MBC), Guy's Hospital. **Recruitment:** Postmenopausal women recruited from GP referrals to osteoporosis unit or from bone clinic. Bone clinic subjects were selected because of their low BMD (T-score≥2 SD below ref mean for young adult women at lumbar spine) and having at least one vertebral deformity previously diagnosed by local hospital. 443 women screened for inclusion.
Number of patients and fractures	Recruited: n=161; Excluded: n=1 (poor DXA image quality) Total, n=161 for per-vertebra analysis; n=160 for per-person analysis Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 1978/2093 (94.5%)
Patient characteristics	**Age (mean):** 64 years (SD 7.1), range 49-81 years **Gender:** 100% women **Ethnicity:** NR **Setting:** Outpatient **Country:** UK **Inclusion criteria:** Referred by GP to osteoporosis unit or from bone clinic. Bone clinic subjects had T-score≥2SD below ref mean. **Exclusion criteria:** Moderate to severe scoliosis apparent on BMD scan or mentioned on previous referral.
Definition of vertebral fracture	Index test: Visual - method unspecified

	Reference test: Visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic QDR-4500A Radiography: Siemens X-ray unit with Polydoros 50 generator			
Index test(s) and reference standard	**Index test** Two lateral DXA with VFA using single- and dual-energy scan HD modes. trained operator split screening GP patients according to visual subjective assessment of VFA images into group A (normal), group B (at least one obvious vertebral deformity), and group C (equivocal, operator uncertain). Group D was (MBC recruits). Recruitment to a group stopped at approximately 50 participants. Reference data for normal vertebral dimensions obtained from 100 women (mean age 63 SD6.9) years). VF diagnosed using Eastell and McCloskey algorithms. **Reference standard** Anteroposterior and lateral thoracolumbar conventional spinal radiograph in left lateral decubitus position, centered at T7 and L3. Radiographs evaluated by experienced radiologist, blinded to VFA results, using VSQ (Genant) method. **Vertebrae range scanned for VFA:** L4-T4 **Time between index and reference test:** DXA with VFA conducted on same day as conventional radiography			
2x2 table	**Grade 1+, per-vertebra analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	154	28	182
	Index test -	45	1751	1796
	Total	199	1779	1978

	Grade 2+, per-vertebra analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	113	69	182
	Index test -	10	1786	1796
	Total	123	1855	1978
	Grade 1+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	47	11	58
	Index test -	13	89	102
	Total	60	100	160
	Grade 2+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	40	18	58
	Index test -	1	101	102
	Total	41	119	160
Statistical measures	**Per-vertebra analysis (n=2083, n=225 with VF Grade≥1)**			

	Sensitivity: 77.4% (95%CI 71.1-82.6) Specificity: 98.4% (95%CI 97.7-98.9) PPV: 84.6% (95%CI 78.7-89.1) NPV: 97.5% (95%CI 96.7-98.1) PLR: 49.2% (95%CI 33.8-71.5) NLR: 0.2% (95%CI 0.2-0.3) AUC: NR Prevalence: 10.1% Note: Calculated from raw data reported in study, excluding unreadable vertebrae. **Per-vertebra analysis (n=2083, n=225 with VF Grade≥2)** Sensitivity: 91.9% (95%CI 85.7-95.5) Specificity: 96.3% (95%CI 95.3-97.1) PPV: 62.1% (95%CI 54.9-68.8) NPV: 99.4% (95%CI 99.0-99.7) PLR: 24.7% (95%CI 19.5-31.3) NLR: 0.1% (95%CI 0.1-0.2) AUC: NR Prevalence: 6.2% Note: Calculated from raw data reported in study, assuming that vertebrae classified as VF Grade 1 are normal and excluding unreadable vertebrae.

	Per-person analysis (n=160, n=60 with VF Grade≥1) Sensitivity: 78.3% (95%CI 66.4-86.9) Specificity: 89.0% (95%CI 81.4-93.7) PPV: 81.0% (95%CI 69.1-89.1) NPV: 87.3% (95%CI 79.4-92.4) PLR: 7.1% (95%CI 4.0-12.6) NLR: 0.24% (95%CI 0.15-0.4) AUC: NR Prevalence: 37.5% Note: Calculated from raw data reported in study. **Per-person analysis (n=160, n=41 with VF Grade≥2)** Sensitivity: 97.6% (95%CI 87.4-99.6) Specificity: 84.9% (95%CI 77.4-90.2) PPV: 69.0% (95%CI 56.2-79.4) NPV: 99.0% (95%CI 94.7-99.8) PLR: 6.5% (95%CI 4.2-9.9) NLR: 0.03% (95%CI 0.0-0.2) AUC: NR Prevalence: 25.6%

	Note: Calculated from raw data reported in study, assuming that vertebrae classified as deformed on DXA with VFA or Grade 1 on conventional radiography are normal and excluding people with unreadable vertebrae.
Source of funding	Not reported
Limitations	Risk of bias: High (Unclear whether consecutive or random selection; case control design; excludes cases of scoliosis; Only one assessor of radiographs) Indirectness: Directly applicable

Rud, 2016

Bibliographic Reference	Rud, B; Vestergaard, A; Hyldstrup, L; Accuracy of densitometric vertebral fracture assessment when performed by DXA technicians--a cross-sectional, multiobserver study.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2016; vol. 27 (no. 4); 1451-1458

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Patients≥65 years-old referred for osteoporosis assessment at Danish clinic **Recruitment:** Consecutive patients referred, mainly by GPs, to clinic invited to participate between 02/2006 to 09/2008. Information about study provided with regular information letter sent to participants prior to clinic visit.
Number of patients and fractures	Recruited: n=303; Excluded: n=4 (n=3 could not be positioned in scanner; n=1 not able to provide informed consent) Total, n=235 (lateral scans of 54 patients were accidently deleted before assessment)

	Total number of adequately visualized vertebrae/total number of evaluable vertebrae: NR
Patient characteristics	**Age (mean):** 74.9 (SD 6.9) **Gender (M/F):** 25/210 **Ethnicity:** NR **Setting:** Outpatient **Country:** Denmark **Inclusion criteria:** referred for osteoporosis assessment **Exclusion criteria:** People with multiple myeloma or malignancies with bone metastases; People who could not be positioned for the lateral scan; people in whom informed consent was not obtainable
Definition of vertebral fracture	Visual semi-quantitative-Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Discovery A Radiography: Optima digital radiographic system
Index test(s) and reference standard	**Index test** Postero-anterior and lateral single energy VFA scan of thoracolumbar spine in supine position (using Physician Viewer software) in addition to routine DXA scan at hip and lumbar spine. Lateral scans evaluated by 6 DXA technicians according to VSQ (Genant) method. Technicians used software for height measurements if visual assessment insufficient. DXA technicians received training sessions in use of software and Genant classification prior to VFA. Technicians counted deformities rather than osteoporosis-related fractures. VF classification conducted blinded to radiological classification. **Reference standard**

	Digital radiograph of thoracolumbar spine in left lateral decubitus position, centered on T7 and L2, independently assessed by 2 radiologists using VSQ (Genant) method. VF classification agreed by consensus. Deformities due to causes other than osteoporosis not counted as fractured. VF classification conducted blinded to VFA classification. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** Digital radiography was to be conducted within 2 weeks of DXA with VFA. Median interval was 8 days, interval<15 days in 75% of patients.			
2x2 table	**Grade 1+, per-person analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	86	19	105
	Index test -	51	79	130
	Total	137	98	235
	Grade 2+, per-person analysis	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	60	21	81
	Index test -	22	132	154
	Total	82	153	235
Statistical measures	**Per-person analysis (n=235, n=137 with VF Grade≥1)** Sensitivity: 63.0% (95%CI 54.7-70.6)			

	Specificity: 81.0% (95%CI 72.1-87.5) PPV: 82.3% (95%CI 73.8-88.4) NPV: 61.0% (95%CI 52.4-69.0) PLR: 3.32% (95%CI 2.16-5.09) NLR: 0.46% (95%CI 0.36-0.58) AUC: NR Prevalence: 58.3% Note: Calculated using number of VF on conventional radiography and reported mean sensitivity/specificity from the 6 DXA technicians. Individual diagnostic accuracy data for each of these technicians has not been extracted. **Per-person analysis (n=235, n=82 with VF Grade≥2)** Sensitivity: 73.0% (95%CI 62.5-81.4) Specificity: 86.0% (95%CI 79.6-90.6) PPV: 73.6% (95%CI 63.2-82.0) NPV: 85.6% (95%CI 79.2-90.3) PLR: 5.21% (95%CI 3.45-7.89) NLR: 0.31% (95%CI 0.22-0.45) AUC: NR Prevalence: 34.9% Note: Calculated using number of VF on conventional radiography and reported mean sensitivity/specificity from the 6 DXA technicians. Individual diagnostic accuracy data for each of these technicians has not been extracted.

Source of funding	Reports no funding was provided for this study
Limitations	Risk of bias: Low Indirectness: Directly applicable

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Osteoporosis Sample size	n = 82 ; % = 35
Osteopenia Sample size	n = 110 ; % = 47

Schousboe, 2006

Bibliographic Reference	Schousboe, John T; Debold, C Rowan; Reliability and accuracy of vertebral fracture assessment with densitometry compared to radiography in clinical practice.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2006; vol. 17 (no. 2); 281-9

Study details

Study type	Cross-sectional study
Study methodology	**Data source:** Women referred for bone densitometry at large multi-specialist group medical practice, suburban Minnespolis, USA **Recruitment:** Entry offered to all women age 65+ years referred for bone densitometry. After 100 participants recruited, entry restricted to women 65+ years with osteopenia or osteoporosis.
Number of patients and fractures	Recruited: n=205; Excluded: n=1 from per-vertebra analysis (lateral absorptiometry image could not be located) and n=2 from per-person analysis (anteroposterior absorptiometry image could not be located) Total, n=204 for per-vertebra analysis and n=203 for per-person analysis Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 2374/2652 (89.5%) for reader 1; 2366/2652 (89.8%) for reader 2
Patient characteristics	**Age (mean):** 74.2 years, range 65-93 years **Gender:** 100% women **Ethnicity:** Caucasian, n=199; African American, n=4; Asian, n=1; mixed ethnicity, n=1 **Setting:** Outpatient **Country:** USA **Inclusion criteria:** women, aged ≥65 years; after 100 participants recruited, osteopenia or osteoporosis **Exclusion criteria:** NR
Definition of vertebral fracture	Visual semi-quantitative-Genant method

Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Delphi W or Delphi C Radiography: not reported, radiographs not digitized			
Index test(s) and reference standard	**Index test** DXA with VFA anteroposterior and lateral single-energy absorptiometry images of thoracolumbar spine. Evaluated by 2 readers (rheumatologist and endocrinologist) on screen (Hologic Physician Viewer) using VSQ (Genant) method. **Reference standard** Lateral thoracolumbar conventional spinal radiographs in left lateral decubitus position, centered on T8 and L3. Evaluated by same 2 readers using VSQ (Genant) method. Readers were blinded to own assessment of radiographs and VFA images. **Vertebrae range scanned for VFA:** T4-L4 **Time between index and reference test:** DXA with VFA on same day as conventional radiography			
2x2 table	**Grade 2+, per-vertebra analysis – Reader 1**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	15	16	31
	Index test -	13	2608	2621
	Total	28	2624	2652
	Grade 2+, per-vertebra analysis – Reader 2	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	11	18	29

	Index test -	10	2613	2623
	Total	21	2631	2652
	Grade 2+, per-person analysis – Reader 1	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	10	13	23
	Index test -	6	174	180
	Total	16	187	203
	Grade 2+, per-person analysis – Reader 2	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	11	13	24
	Index test -	3	176	179
	Total	14	189	203
Statistical measures	**Per-vertebra analysis (Reader 1; n=2652, n=28 with VF Grade≥2)** Sensitivity: 53.6% (95%CI 35.8-70.5) Specificity: 99.4% (95%CI 99.0-99.6) PPV: 48.4% (95%CI 32.0-65.2) NPV: 99.5% (95%CI 99.2-99.7)			

	PLR: 87.9% (95%CI 48.3-159.8) NLR: 0.5% (95%CI 0.3-0.7) AUC: NR Prevalence: 1.1% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity, including unreadable vertebrae which were treated as normal. **Per-vertebra analysis (Reader 2; n=2652, n=21 with VF Grade≥2)** Sensitivity: 52.4% (95%CI 32.4-71.7) Specificity: 99.3% (95%CI 98.9-99.6) PPV: 37.9% (95%CI 22.7-56.0) NPV: 99.6% (95%CI 99.3-99.8) PLR: 76.6% (95%CI 41.4-141.6) NLR: 0.5% (95%CI 0.3-0.8) AUC: NR Prevalence: 0.79% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity, , including unreadable vertebrae which were treated as normal. **Per-person analysis (Reader 1; n=203 participants, n=16 with VF Grade≥2)** Sensitivity: 62.5% (95%CI 38.6-81.5) Specificity: 93.1% (95%CI 88.5-95.9)

	PPV: 43.5% (95%CI 25.6-63.2) NPV: 96.7% (95%CI 92.9-98.5) PLR: 9.0% (95%CI 4.7-17.2) NLR: 0.4% (95%CI 0.2-0.8) AUC: NR Prevalence: 7.9% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity. **Per-person analysis (Reader 2; n=203 participants, n=14 with VF Grade≥2)** Sensitivity: 78.6% (95%CI 52.4-92.4) Specificity: 93.1% (95%CI 88.6-95.9) PPV: 45.8% (95%CI 27.9-64.9) NPV: 98.3% (95%CI 95.2-99.4) PLR: 11.4% (95%CI 6.3-20.6) NLR: 0.2% (95%CI 0.1-0.6) AUC: NR Prevalence: 6.9% Note: data for diagnosis of VF Grade≥1 was not extracted because number of vertebrae/people with VF not reported for this categorization
Source of funding	Funded by grant from Hologic Inc. and the Park Nicollet Institute

Limitations	Risk of bias: High (Recruitment strategy changed after first 100 women were recruited and restricted to women with ostopenia and osteoporosis) Indirectness: Directly applicable

Sullivan, 2011

Bibliographic Reference	Sullivan, Sarah; Wagner, Julie; Resnick, Neil M; Nelson, Joel; Perera, Subashan K; Greenspan, Susan L; Vertebral fractures and the misclassification of osteoporosis in men with prostate cancer.; Journal of clinical densitometry: the official journal of the International Society for Clinical Densitometry; 2011; vol. 14 (no. 3); 348-53

Study details

Study type	Prospective cohort study
Study methodology	**Data source:** Men with non-metastatic prostate cancer recruited from physicians in Pittsburgh, Pennsylvania, USA **Recruitment:** Participants screened via telephone and gave written informed consent.
Number of patients and fractures	Recruited: n=116; Excluded: n=0 Total, n=116 Total number of adequately visualized vertebrae/total number of evaluable vertebrae: NR
Patient characteristics	**Age (mean):** 75 years **Gender:** 100% men **Ethnicity:** NR

	Setting: Outpatient **Country:** USA **Inclusion criteria:** male, aged ≥60 years, non-metastatic prostate cancer, receiving androgen-deprivation therapy (ADT) for ≥6-mo (with or without anti-androgen) **Exclusion criteria:** metastatic prostate cancer, had non-metastatic prostate cancer with prostate-specific antigen level>4 (unless undergoing adjustments to therapy), used medications known to alter bone mineral metabolism within past year **Participants receiving steroids at baseline:** 0/116 (0%)			
Definition of vertebral fracture	Visual semi-quantitative-Genant method			
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Discovery A Radiography: not reported			
Index test(s) and reference standard	**Index test** DXA of hip, umbar spine, and 1/3 distal radius with lateral spine single-energy VFA, evaluated by technician using VSQ (Genant) method. **Reference standard** Lateral thoracolumbar conventional spinal radiograph performed by single radiologist using VSQ (Genant) method. **Vertebrae range scanned for VFA:** T5-L4 **Time between index and reference test:** unclear, not reported			
2x2 table	**Grade 1+, per-person analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**

	Index test +	38	4	42
	Index test -	0	74	74
	Total	38	78	116
Statistical measures	**Per-person analysis (n=116 participants, n=38 with VF Grade≥1)** Sensitivity: 100.0% (95%CI 90.8-100.0) Specificity: 94.9% (95%CI 87.5-98.0) PPV: 90.5% (95%CI 77.9-96.2) NPV: 100.0% (95%CI 95.1-100.0) PLR: 19.5% (95%CI 7.5-50.7) NLR: not estimable AUC: NR Prevalence: 32.8% Note: Calculated using reported number of VF on conventional radiography and reported sensitivity/specificity.			
Source of funding	Grants 2K24DK062895-06, PC060710 (DOD IDEA), University of Pittsburgh Clinical Translational Research Center, RFA-RM-06-002, Claude D. Pepper Center, Division of Geriatric Medicine 2 P30 AG024827-06, University of Pittsburgh Department of Urology, the Hollerand Family			
Limitations	Risk of bias: High (Insufficient information about recruitment; unclear whether assessors blinded to results of other tests; unclear when conventional radiography conducted; Only one assessor of radiographs) Indirectness: Directly applicable			

van Dort, 2018

Bibliographic Reference	van Dort, M J; Romme, E A P M; Smeenk, F W J M; Geusens, P P P M; Wouters, E F M; van den Bergh, J P; Diagnosis of vertebral deformities on chest CT and DXA compared to routine lateral thoracic spine X-ray.; Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2018; vol. 29 (no. 6); 1285-1293

Study details

Study type	Retrospective cohort study
Study methodology	**Data source:** Participants in clinical trial of COPD-related osteoporosis **Recruitment:** Data of subjects included in clinical trial at Catharina Hospital, Eindhoven, Netherlands from February 2010-September 2011 (approved by medical ethical committee M09-1971). Subjects included if there was complete availability of X-ray, chest CT, and DXA with VFA.
Number of patients and fractures	Recruited: n=102; Excluded: n=15 (incomplete X-ray, CCT or DXA records) Total, n=87 For DXA with VFA v conventional radiography as reference standard: Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 631/874 (72.2%) For DXA with VFA v chest CT as reference standard: Total number of adequately visualized vertebrae/total number of evaluable vertebrae: 640/874 (73.3%)
Patient characteristics	**Age (mean):** 64.5 years (SD 7.1) **Gender (M/F):** 50/37 **Ethnicity:** NR

	Setting: Clinical **Country:** Netherlands **Inclusion criteria:** participating in clinical trial, Caucasian, male, or postmenopausal females aged≥50 years, moderate to severe chronic obstructive pulmonary disease (GOLD definition), osteoporosis, or normal BMD, with or without vertebral deformities; age-matched controls without COPD **Exclusion criteria:** incomplete X-ray, chest CT, or DXA records **Participants receiving steroids at baseline:** NR
Definition of vertebral fracture	Visual semi-quantitative-Genant method
Densitometric, radiographic or CT hardware used	DXA with VFA: Hologic Discovery A Radiography: Philips Brilliance 64 Chest CT: Philips iCT 256
Index test(s) and reference standard	**Index test** Lateral DXA with single-energy VFA semi-automatic SpineAnalyzer software for morphometry; VF then diagnosed according to Genant method. After manual adjustment, software calculates outcomes. Evaluated in random order by one experienced operator and subsequently again within 6 weeks. Vertebral levels checked across scanning modalities. DXA images digitally available as Dicom files. Evaluated by one experienced operator. **Reference standard** - Lateral thoracolumbar conventional spinal radiographs using digital radiography (Digital Diagnost). X-ray images digitally available as Dicom files. VF diagnosed using VSQ (Genant) method. Evaluated by same experienced operator as DXA with VFA.

	- Chest CT. To combine information of the sagittal reformats and to mimic visualisation of vertebrae on X-ray and DXA, all sagittal reformats containing spine superposed into one image: contrast was adjusted in the reformats to (partly) eliminate soft tissue, after which sagittal reformats were superposed to create simulated X-ray images based on CCT using Matlab version R2013a (MathWorks®). Evaluated by same experienced operator as DXA with VFA. **Vertebrae range scanned for VFA:** T4-L1 **Time between index and reference test:** Conventional radiography and chest CT conducted at same time. DXA with VFA conducted average time 157.7 days (SD 166.6) after conventional radiography/chest CT.
Statistical measures	**Per-vertebra analysis for DXA with VFA v Conventional radiography (reference standard) (n=631, n=51 with VF Grade≥1 on conventional radiography)** Sensitivity: 51.0% (95%CI 37.7-64.1) Specificity: 97.1% (95%CI 95.4-98.2) PPV: 60.5% (95%CI 45.6-73.6) NPV: 95.7% (95%CI 93.8-97.1) PLR: 17.4% (95%CI 10.1-29.9) NLR: 0.5% (95%CI 0.4-0.7) AUC: 0.74 (95%CI 0.65-0.83) Prevalence: 8.1% Note: Outcome measures calculated using reported number of VF on conventional radiography and reported sensitivity/specificity. As such, outcome measures here may differ slightly from those reported in study. **Per-vertebra analysis for DXA with VFA v Chest CT (reference standard) (n=631, n=60 with VF Grade≥1 on chest CT)** Sensitivity: 56.7% (95%CI 44.1-68.4)

Specificity: 97.1% (95%CI 95.4-98.2)

PPV: 66.7% (95%CI 53.0-78.0)

NPV: 95.6% (95%CI 93.6-97.0)

PLR: 19.3% (95%CI 11.5-32.5)

NLR: 0.5% (95%CI 0.3-0.6)

AUC: 0.8 (95%CI 0.7-0.9)

Prevalence: 9.4%

Note: Outcome measures calculated using reported number of VF on chest CT and reported sensitivity/specificity. As such, outcome measures here may differ slightly from those reported in study.

Per-vertebra analysis for DXA with VFA v Conventional radiography (reference standard) (n=631, n=25 with VF Grade≥2 on conventional radiography)

Sensitivity: 44.0% (95%CI 26.7-62.9)

Specificity: 99.0% (95%CI 97.9-99.6)

PPV: 64.7% (95%CI 41.3-82.7)

NPV: 97.7% (95%CI 96.2-98.6)

PLR: 44.4% (95%CI 17.9-110.5)

NLR: 0.6% (95%CI 0.4-0.8)

AUC: 0.72 (95%CI 0.59-0.84)

Prevalence: 3.96%

Note: Outcome measures calculated using reported number of VF on conventional radiography and reported sensitivity/specificity. As such, outcome measures here may differ slightly from those reported in study.

	Per-vertebra analysis for DXA with VFA v Chest CT (reference standard) (n=640, n=26 with VF Grade≥2 on chest CT) Sensitivity: 42.3% (95%CI 25.5-61.1) Specificity: 99.0% (95%CI 97.9-99.6) PPV: 64.7% (95%CI 41.3-82.7) NPV: 97.6% (95%CI 96.1-98.5) PLR: 43.3% (95%CI 17.4-108.0) NLR: 0.6% (95%CI 0.4-0.8) AUC: 0.71 (95%CI 0.58-0.83) Prevalence: 4.06% Note: Outcome measures calculated using reported number of VF on chest CT and reported sensitivity/specificity. As such, outcome measures here may differ slightly from those reported in study.
Source of funding	Funded by Stichting De Weijerhorst
Limitations	Risk of bias: High (Not clear whether consecutive or random sample; average time between DXA with VFA scan and reference standard>5-mo; Only one assessor of radiographs/chest CT) Indirectness: Directly applicable

Characteristics

Study-level characteristics

Characteristic	Study (N = 87)
Osteoporosis Sample size	n = 40 ; % = 46
Normal BMD Sample size	n = 47 ; % = 54
COPD Sample size	n = 57 ; % = 65.5
No COPD Sample size	n = 30 ; % = 34.5

Vokes 2003

Bibliographic Reference	Vokes, Tamara J; Dixon, Larry B; Favus, Murray J; Clinical utility of dual-energy vertebral assessment (DVA).; Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2003; vol. 14 (no. 11); 871-8

Study details

Study type	Prospective cohort study unclear when index and reference tests conducted

Study methodology	**Data source:** Subjects referred to University of Chicago Bone Program for routine BMD measurement **Recruitment:** Participants were referred and agreed to participate in study. Subset of participants received both DXA with VFA and conventional radiography.
Number of patients and fractures	Recruited: n=297; Excluded: n=231 (no explanation provided as to why these participants did not receive conventional radiography) Total, n=66 received both DXA with VFA and conventional radiography (but 1 participant subsequently excluded due to unreadable vertebrae on radiography) Total number of adequately visualized vertebrae/total number of evaluable vertebrae: NR
Patient characteristics	**Age (mean):** 64.0 years (SD 13.0) (recruited participants) **Gender (M/F):** 25/272 (recruited participants) **Ethnicity:** African American, n=70; Asian, n=6; Caucasian, n=216; Hispanic, n=5 (eligible participants) **Setting:** Outpatient **Country:** USA **Inclusion criteria:** referred for routine BMD measurement **Exclusion criteria:** NR
Definition of vertebral fracture	Visual assessment then quantitative morphometry (25% height reduction, equivalent to Genant Grade 2+) if suspected VF
Densitometric, radiographic or CT hardware used	DXA with VFA: GE Lunar Prodigy Radiography: not reported, used standardized protocol

Index test(s) and reference standard	**Index test** Left lateral decubitus DXA in supine position with dual-energy VFA (referred to as 'Instant Vertebral Assessment'), evaluated by endocrinologist (trained in densitometry but not radiology). Vertebral fracture defined as anterior-posterior vertebral height ratio ≤0.75. Vertebrae judged abnormal by endocrinologist, blinded to radiograph interpretation, on visual inspection was adjusted using scanner software. **Reference standard** Thoracolumbar conventional spinal radiograph as part of routine medical care or other studies. For participants with anatomical abnormalities (for example, scoliosis) repositioning and translucent sponges used during radiography. Images evaluated by skeletal radiologist blinded to VFA interpretation. Vertebral fracture defined as anterior:posterior vertebral height ratio ≤0.75. **Vertebrae range scanned for VFA:** T6-L4 **Time between index and reference test:** unclear, reports participants had conventional radiography "in course of their routine medical care, or as a part of other studies"			
2x2 table	**Grade 2+, per-person analysis**	**Reference standard +** X-ray	**Reference standard –** X-ray	**Total**
	Index test +	20	8	28
	Index test -	1	36	37
	Total	21	44	65
Statistical measures	**Per-person analysis (n=65 participants, n=26 with VF Grade≥2)** Sensitivity: 95.2% (95%CI 77.3-99.2) Specificity: 81.8% (95%CI 68.0-90.5)			

	PPV: 71.4% (95%CI 52.9-84.7) NPV: 97.3% (95%CI 86.2-99.5) PLR: 5.2% (95%CI 2.8-9.9) NLR: 0.1% (95%CI 0.0-0.4) AUC: NR Prevalence: 32.3% Note: Calculated using raw data reported in study.
Source of funding	Supported by Grant AR42739/4A2 S1 from National Institutes of Health and unrestricted educational grant from the Fred and Susan Novy Family Foundation.
Limitations	Risk of bias: High (Unclear why 66/297 participants had both DXA with VFA and conventional radiography; unclear when conventional radiography was conducted; Only one assessor of radiographs) Indirectness: Directly applicable

Appendix E Forest plots

E.1 What is the diagnostic accuracy of DXA-based VFA scan or imaging for identifying vertebral fractures?

E.1.1 DXA with VFA compared to expert radiological assessment of conventional radiography

E.1.1.1 Per-vertebra analysis

Figure 2: DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+ with subgroups by type of VFA scan

Study	TP	FP	FN	TN	Type of VFA scan	Sensitivity (95% CI)	Specificity (95% CI)
Fuerst 2009	76	22	33	2139	Single or dual energy	0.70 [0.60, 0.78]	0.99 [0.98, 0.99]
Diacinti 2012b	410	10	32	11638	Single energy	0.93 [0.90, 0.95]	1.00 [1.00, 1.00]
Hospers 2009	135	24	26	2682	Single energy	0.84 [0.77, 0.89]	0.99 [0.99, 0.99]
Damiano 2006	120	25	25	1484	Single energy	0.83 [0.76, 0.89]	0.98 [0.98, 0.99]
Deleskog 2016	108	30	35	195	Single energy	0.76 [0.68, 0.82]	0.87 [0.82, 0.91]
Domiciano 2013	167	47	61	4952	Single energy	0.73 [0.67, 0.79]	0.99 [0.99, 0.99]
van Dort 2018	26	17	25	563	Single energy	0.51 [0.37, 0.65]	0.97 [0.95, 0.98]
Mazzaferro 2006	49	5	0	635	Single + dual energy	1.00 [0.93, 1.00]	0.99 [0.98, 1.00]
Ferrar 2003	271	25	24	471	Single + dual energy	0.92 [0.88, 0.95]	0.95 [0.93, 0.97]
Ferrar 2000 cohort	250	31	55	580	Single + dual energy	0.82 [0.77, 0.86]	0.95 [0.93, 0.97]
Rea 2000b	154	28	45	1751	Single + dual energy	0.77 [0.71, 0.83]	0.98 [0.98, 0.99]
Ferrar 2000 cross sectional	13	41	10	1317	Single + dual energy	0.57 [0.34, 0.77]	0.97 [0.96, 0.98]
Diacinti 2012a	228	4	3	4315	Dual energy	0.99 [0.96, 1.00]	1.00 [1.00, 1.00]
Binkley 2005	28	30	12	764	Dual energy	0.70 [0.53, 0.83]	0.96 [0.95, 0.97]
Bazzocchi 2012	28	13	12	761	Dual energy	0.70 [0.53, 0.83]	0.98 [0.97, 0.99]
Lin 2017	27	21	15	735	Dual energy	0.64 [0.48, 0.78]	0.97 [0.96, 0.98]

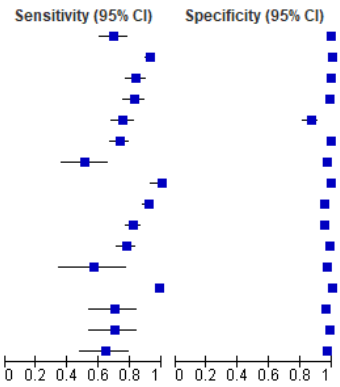
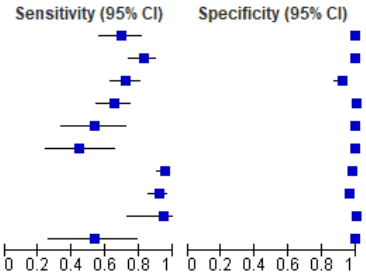


Figure 3: DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+ with subgroups by type of VFA scan

Study	TP	FP	FN	TN	Type of VFA scan	Sensitivity (95% CI)	Specificity (95% CI)
Fuerst 2009	39	22	17	2192	Single or dual energy	0.70 [0.56, 0.81]	0.99 [0.98, 0.99]
Damiano 2006	82	11	17	1544	Single energy	0.83 [0.74, 0.90]	0.99 [0.99, 1.00]
Deleskog 2016	78	22	30	238	Single energy	0.72 [0.63, 0.80]	0.92 [0.87, 0.95]
Domiciano 2013	61	9	33	5124	Single energy	0.65 [0.54, 0.74]	1.00 [1.00, 1.00]
Schousboe 2006	15	16	13	2608	Single energy	0.54 [0.34, 0.72]	0.99 [0.99, 1.00]
van Dort 2018	11	6	14	600	Single energy	0.44 [0.24, 0.65]	0.99 [0.98, 1.00]
Ferrar 2003	153	13	8	617	Single + dual energy	0.95 [0.90, 0.98]	0.98 [0.96, 0.99]
Rea 2000b	113	69	10	1786	Single + dual energy	0.92 [0.86, 0.96]	0.96 [0.95, 0.97]
Binkley 2005	17	1	1	815	Dual energy	0.94 [0.73, 1.00]	1.00 [0.99, 1.00]
Bazzocchi 2012	8	3	7	796	Dual energy	0.53 [0.27, 0.79]	1.00 [0.99, 1.00]



E.1.1.2 Per-person analysis

Figure 4: DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+ with subgroups by type of VFA scan

Study	TP	FP	FN	TN	Type of VFA scan	Sensitivity (95% CI)	Specificity (95% CI)
Sullivan 2011	38	4	0	74	Single energy	1.00 [0.91, 1.00]	0.95 [0.87, 0.99]
Diacinti 2012b	246	0	5	679	Single energy	0.98 [0.95, 0.99]	1.00 [0.99, 1.00]
Damiano 2006	48	8	3	39	Single energy	0.94 [0.84, 0.99]	0.83 [0.69, 0.92]
Ferrar 2008 high risk	72	7	14	205	Single energy	0.84 [0.74, 0.91]	0.97 [0.93, 0.99]
Domiciano 2013	103	22	23	281	Single energy	0.82 [0.74, 0.88]	0.93 [0.89, 0.95]
Lee 2014	35	11	12	42	Single energy	0.74 [0.60, 0.86]	0.79 [0.66, 0.89]
Ferrar 2008 low risk	37	11	15	396	Single energy	0.71 [0.57, 0.83]	0.97 [0.95, 0.99]
Chapurlat 2006	30	11	13	31	Single energy	0.70 [0.54, 0.83]	0.74 [0.58, 0.86]
Rud 2016	86	19	51	79	Single energy	0.63 [0.54, 0.71]	0.81 [0.71, 0.88]
Mazzaferro 2006	17	0	0	36	Single + dual energy	1.00 [0.80, 1.00]	1.00 [0.90, 1.00]
Rea 2000b	47	11	13	89	Single + dual energy	0.78 [0.66, 0.88]	0.89 [0.81, 0.94]
Diacinti 2012a	122	3	4	221	Dual energy	0.97 [0.92, 0.99]	0.99 [0.96, 1.00]
Bazzocchi 2012	19	4	7	38	Dual energy	0.73 [0.52, 0.88]	0.90 [0.77, 0.97]

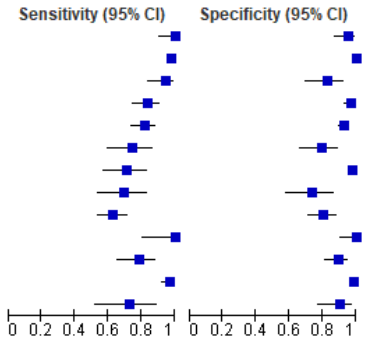
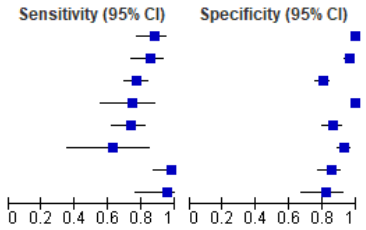


Figure 5: DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+ with subgroups by type of VFA scan

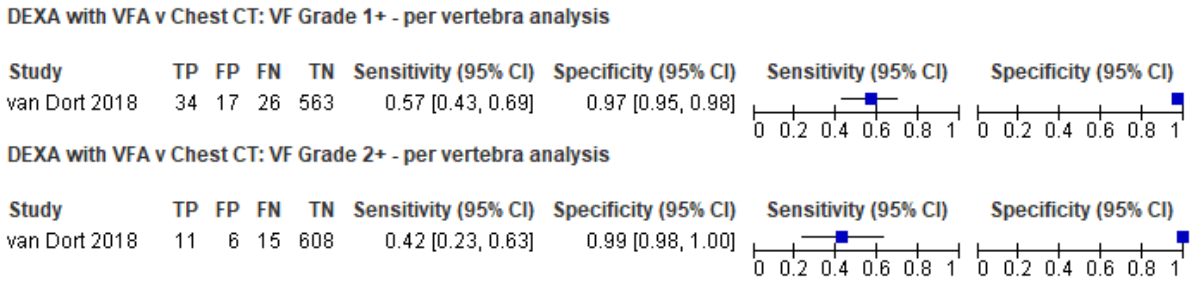
Study	TP	FP	FN	TN	Type of VFA scan	Sensitivity (95% CI)	Specificity (95% CI)
Domiciano 2013	57	1	8	363	Single energy	0.88 [0.77, 0.95]	1.00 [0.98, 1.00]
Ferrar 2008 high risk	51	9	9	229	Single energy	0.85 [0.73, 0.93]	0.96 [0.93, 0.98]
Malgo 2017	102	82	30	328	Single energy	0.77 [0.69, 0.84]	0.80 [0.76, 0.84]
Ferrar 2008 low risk	23	2	8	426	Single energy	0.74 [0.55, 0.88]	1.00 [0.98, 1.00]
Rud 2016	60	21	22	132	Single energy	0.73 [0.62, 0.82]	0.86 [0.80, 0.91]
Schousboe 2006	10	13	6	174	Single energy	0.63 [0.35, 0.85]	0.93 [0.88, 0.96]
Rea 2000b	40	18	1	101	Single + dual energy	0.98 [0.87, 1.00]	0.85 [0.77, 0.91]
Vokes 2003	20	8	1	36	Dual energy	0.95 [0.76, 1.00]	0.82 [0.67, 0.92]



E.1.2 DXA with VFA compared to expert radiological assessment of chest computed tomography

E.1.2.1 Per-vertebra analysis

Figure 6: DXA with VFA compared to expert radiological assessment of chest computed tomography for diagnosis of vertebral fracture



E.2 What is the clinical and cost-effectiveness of VFA with DXA (DXA scan) for identifying people with a vertebral fracture?

No evidence was identified for this evidence review.

Appendix F ROC plots

F.1 DXA with VFA compared to expert radiological assessment of conventional radiography

F.1.1 Per-vertebra analysis

Grade 1+ vertebral fractures

Figure 7: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+ - per-vertebra analysis

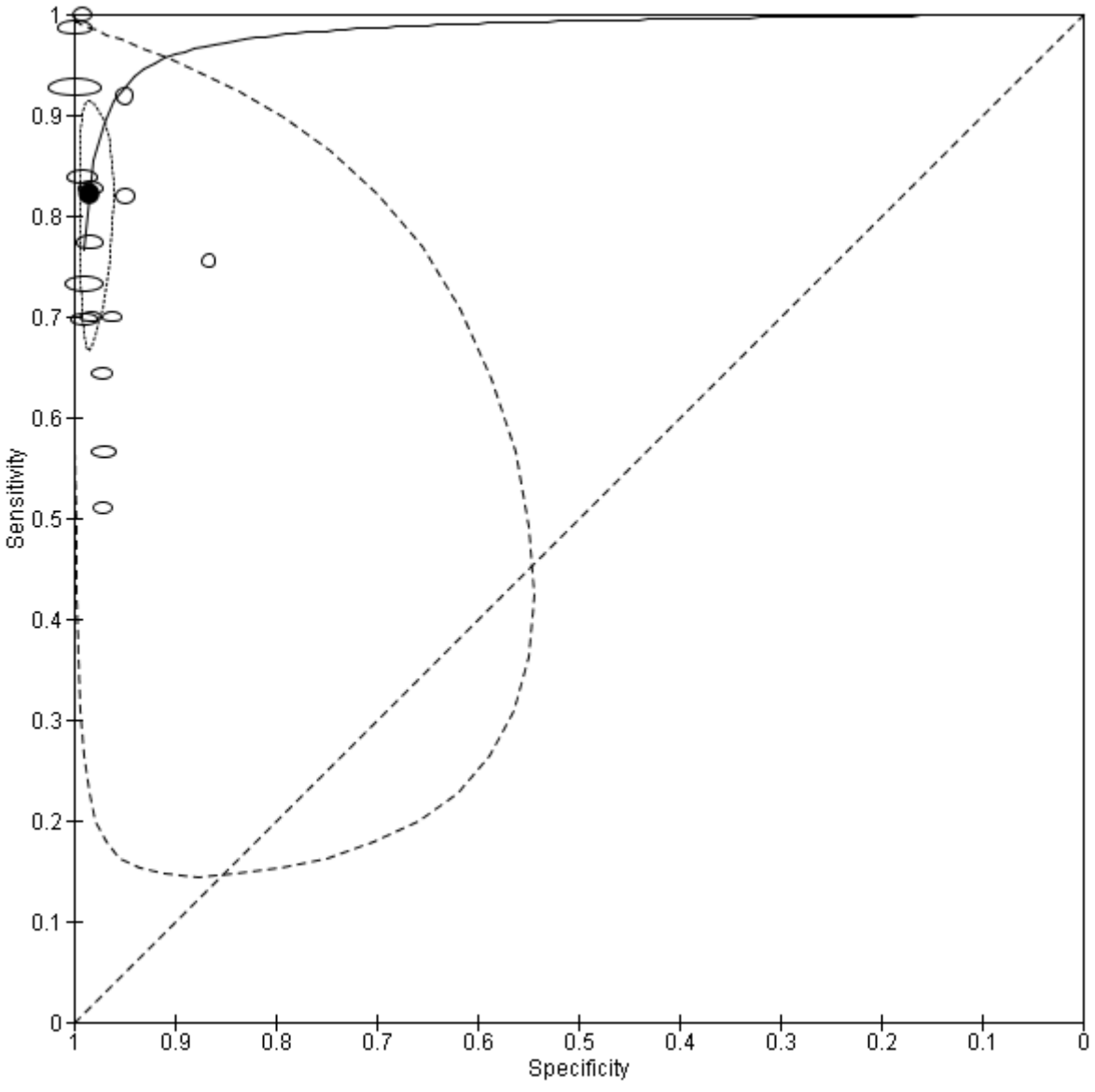


Figure 8: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+: per-vertebra subgroup analysis by type of VFA scan

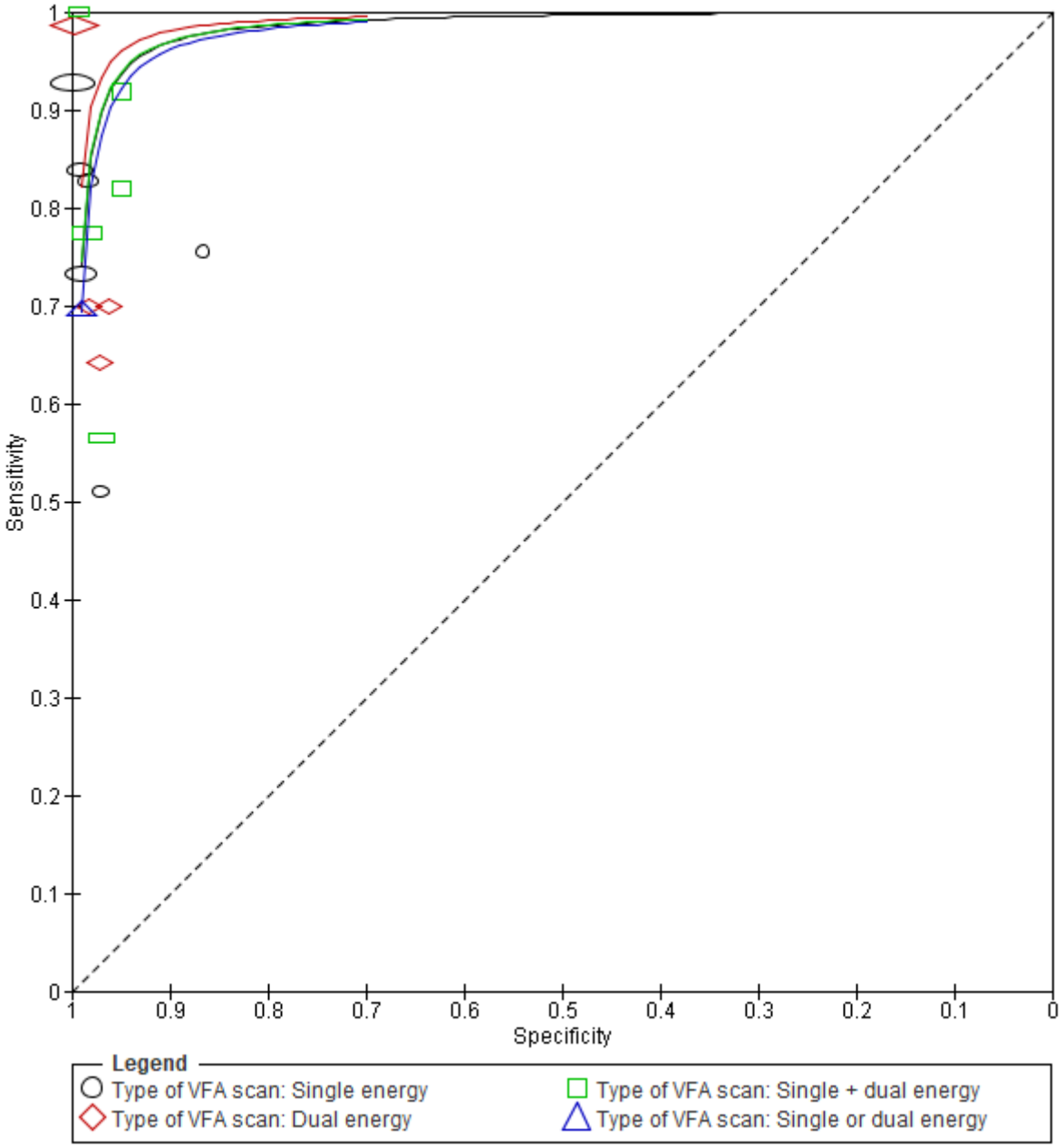


Figure 9: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+: per-vertebra subgroup analysis - Single-energy VFA

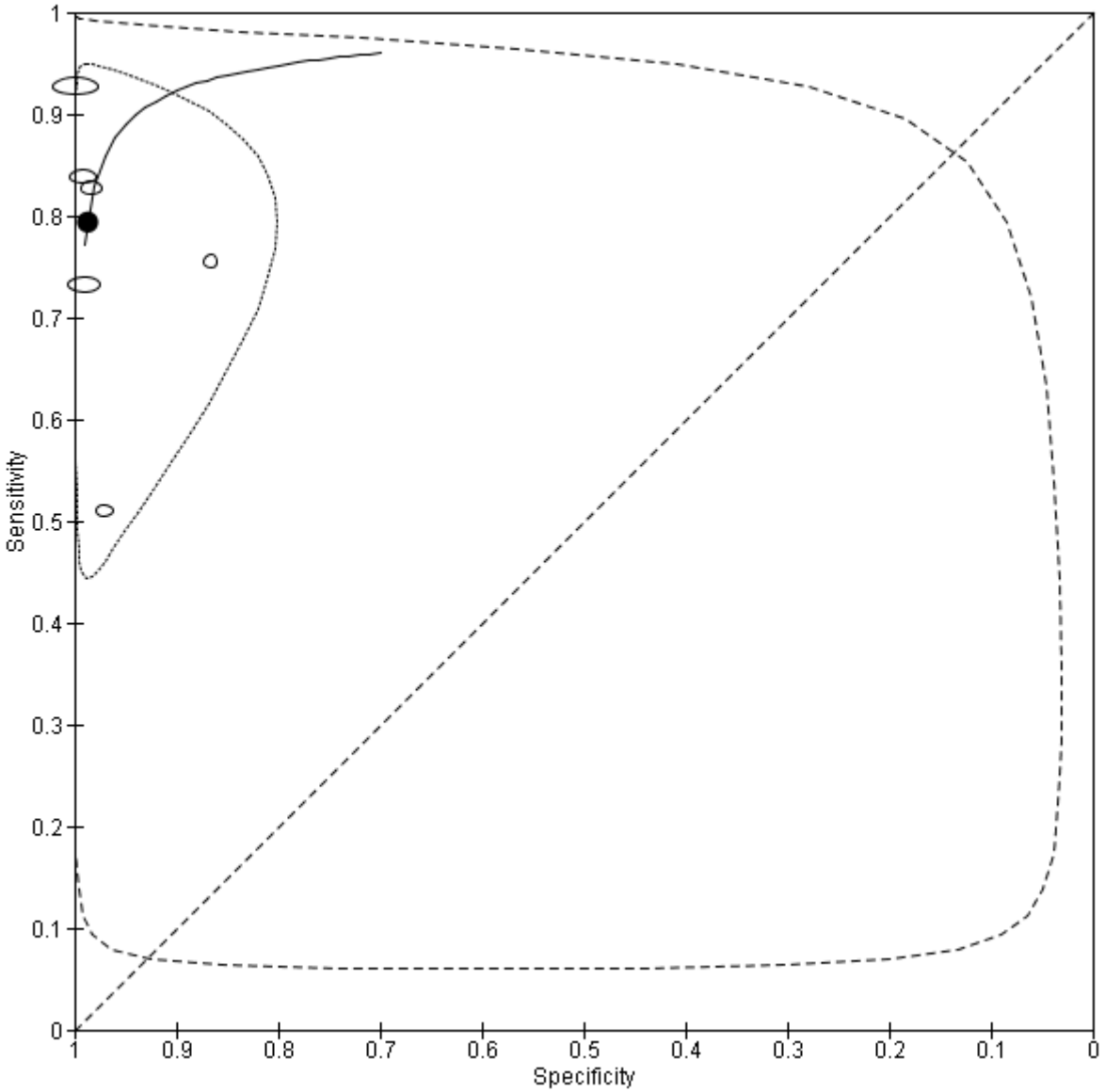


Figure 10: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+: per-vertebra subgroup analysis – Dual-energy VFA

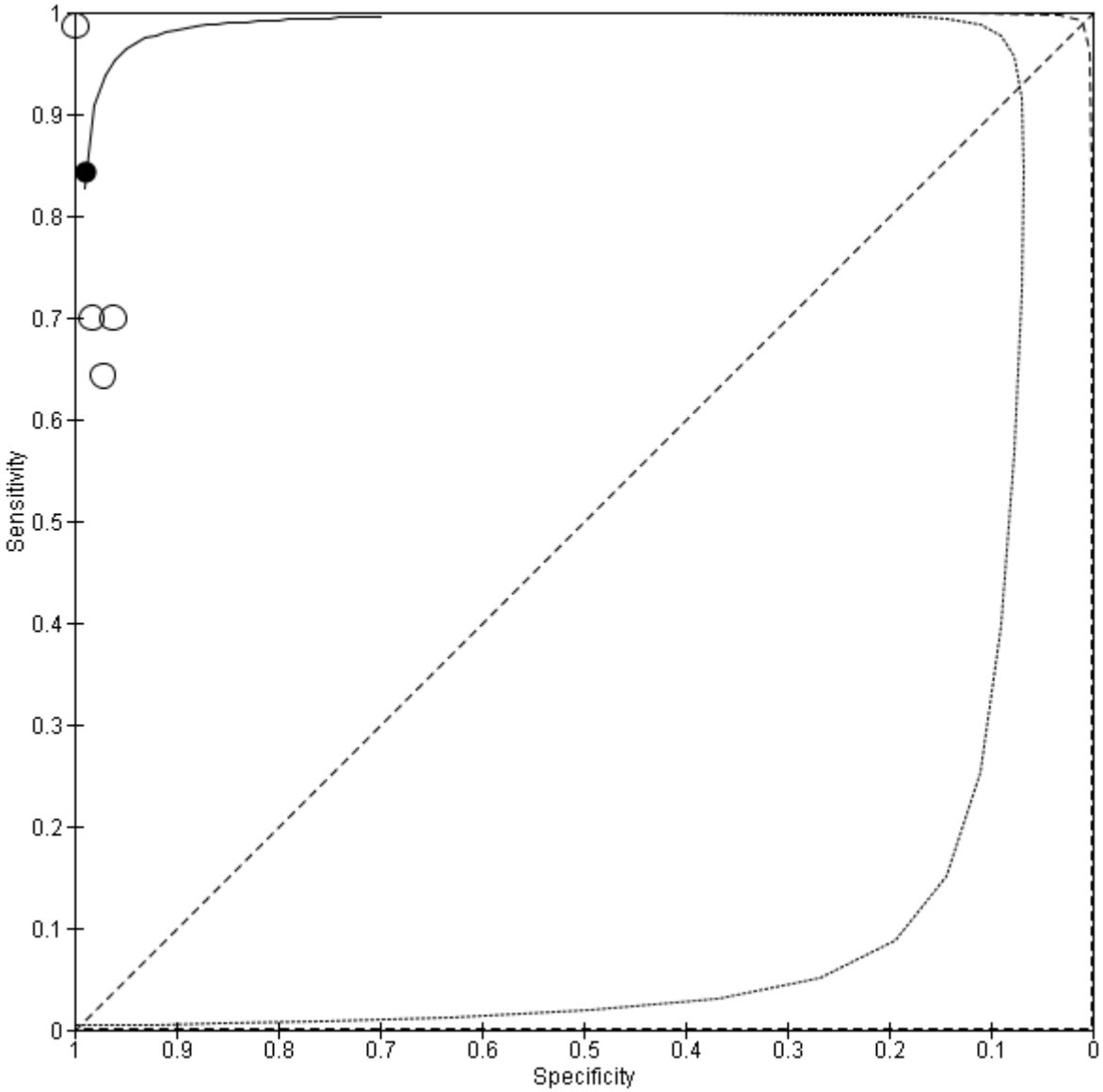
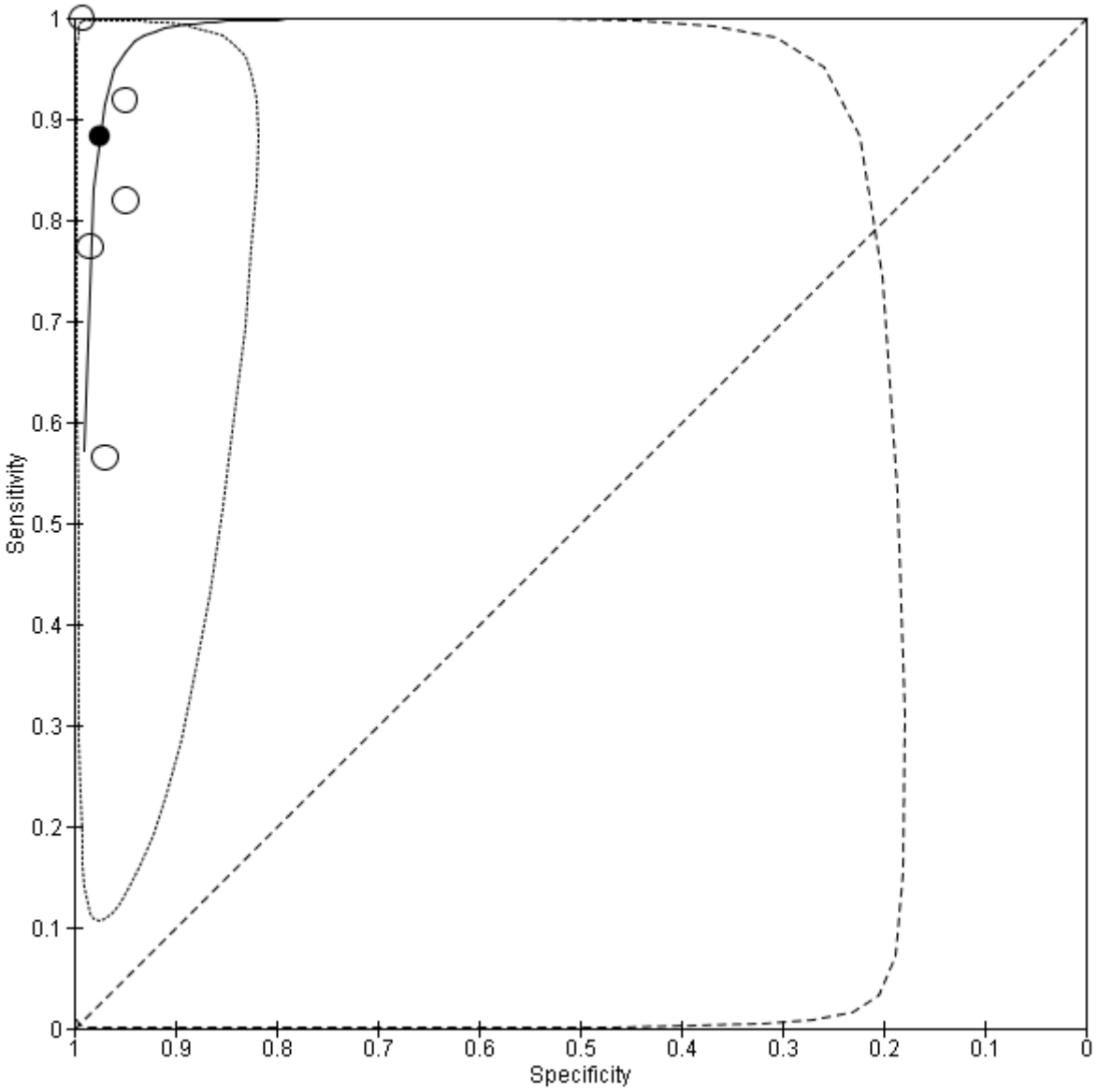
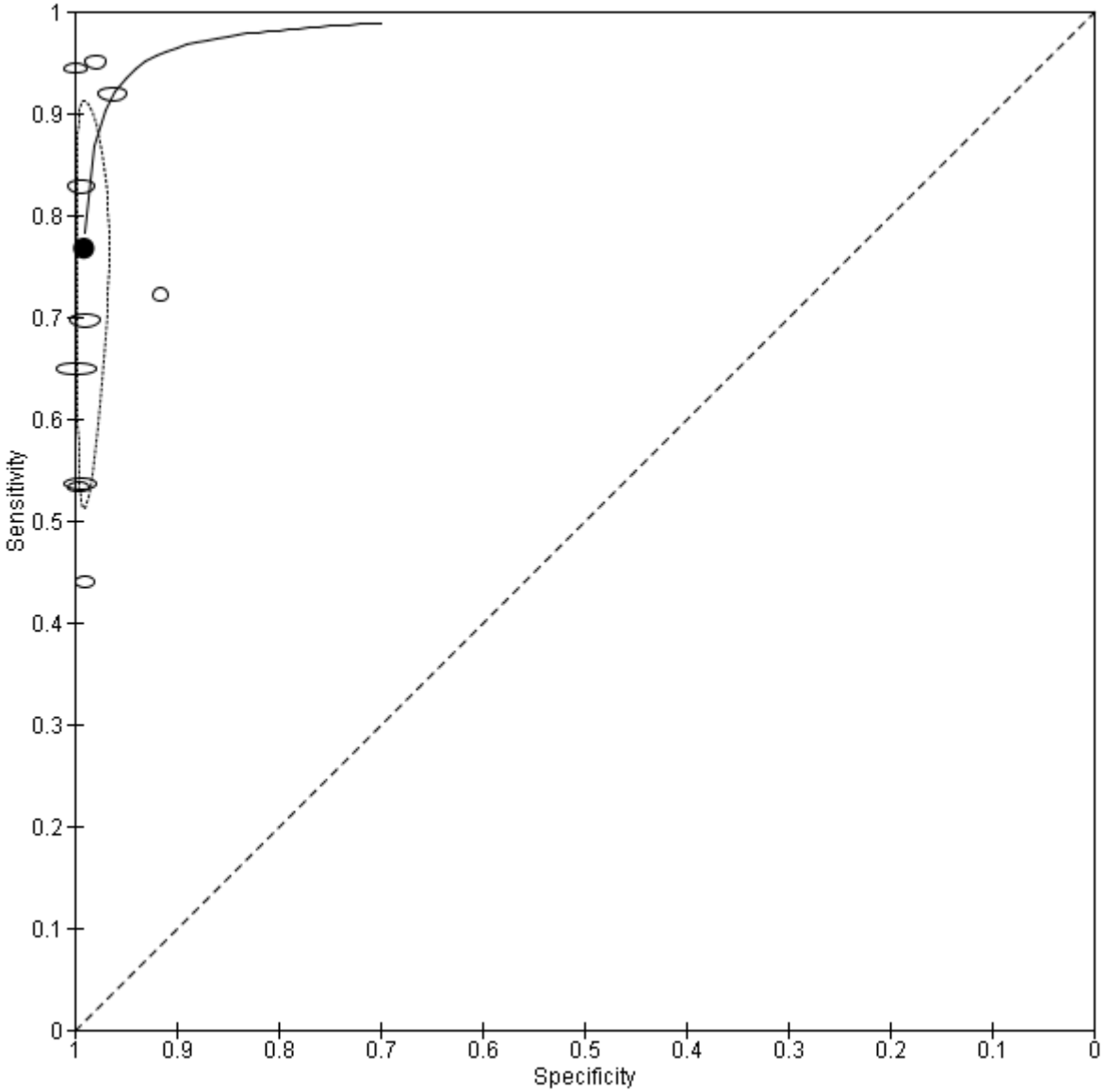


Figure 11: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+: per-vertebra subgroup analysis - Single- and dual-energy VFA



Grade 2+ vertebral fractures

Figure 12: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+ - per vertebra analysis



Note: Prediction region not obtainable for this analysis.

Figure 13: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+: subgroup analysis by type of VFA scan

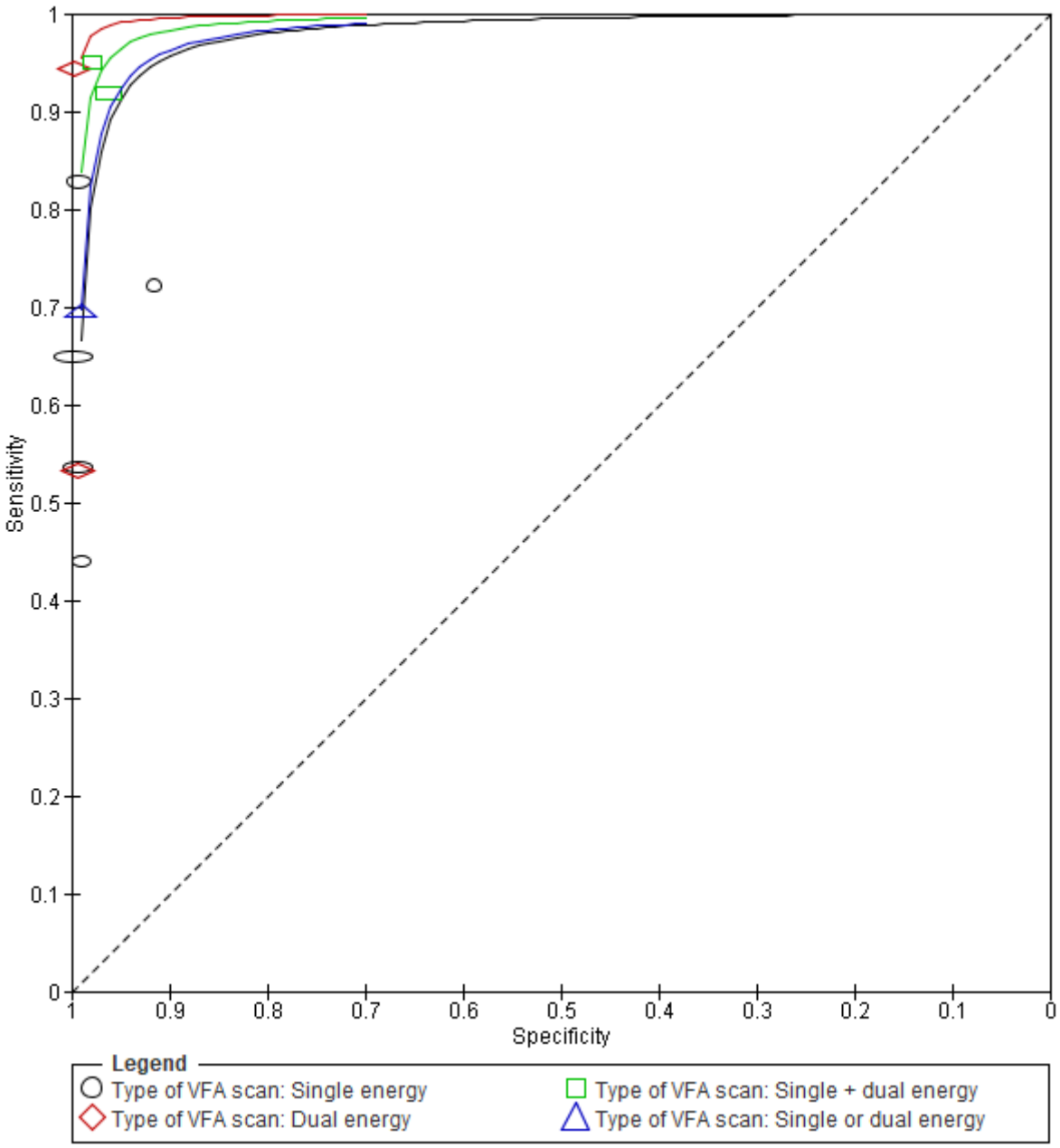
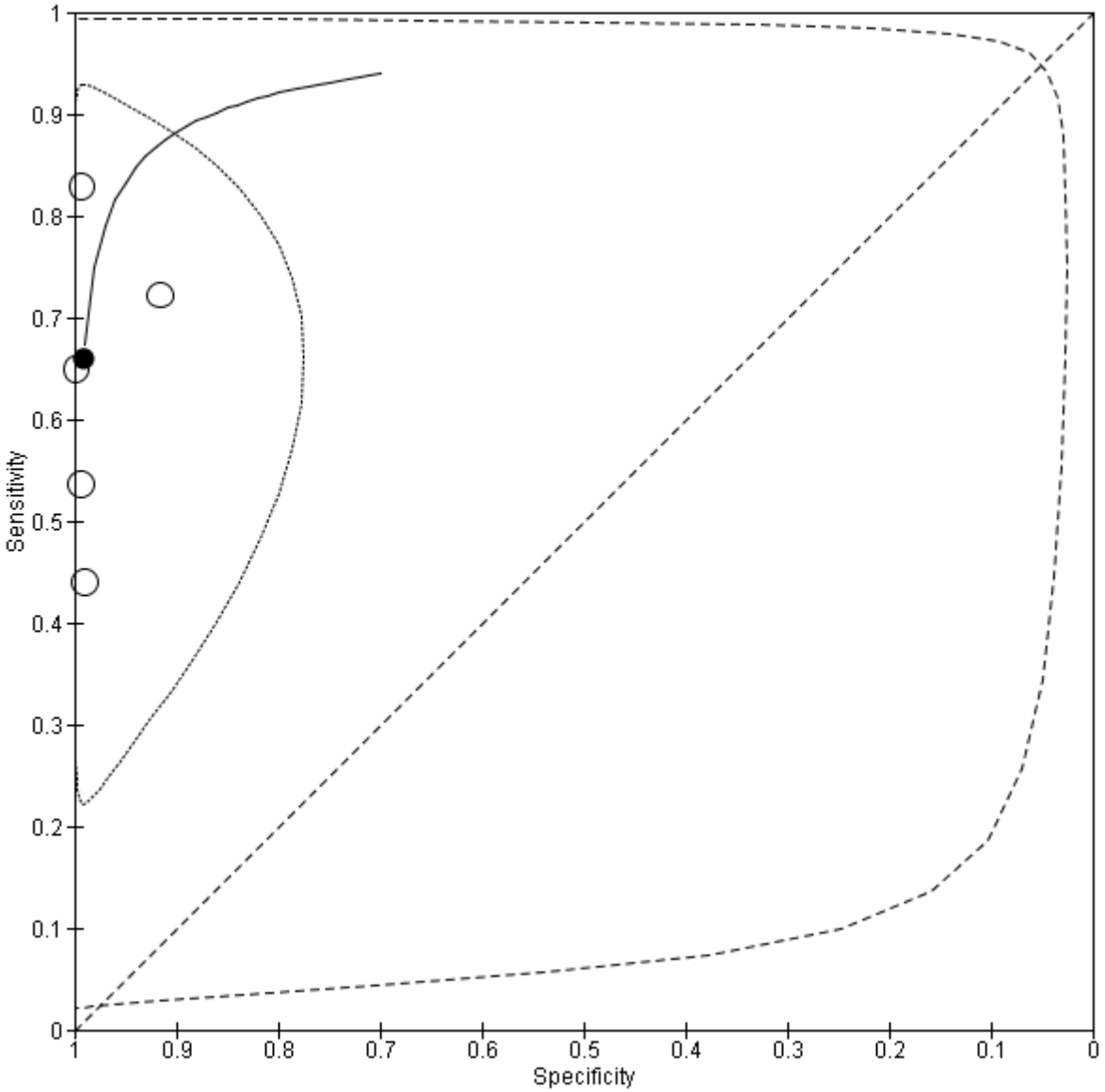


Figure 14: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+: subgroup analysis - Single-energy VFA



F.1.1.1 Per-person analysis

Grade 1+ vertebral fractures

Figure 15: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+ - per-person analysis

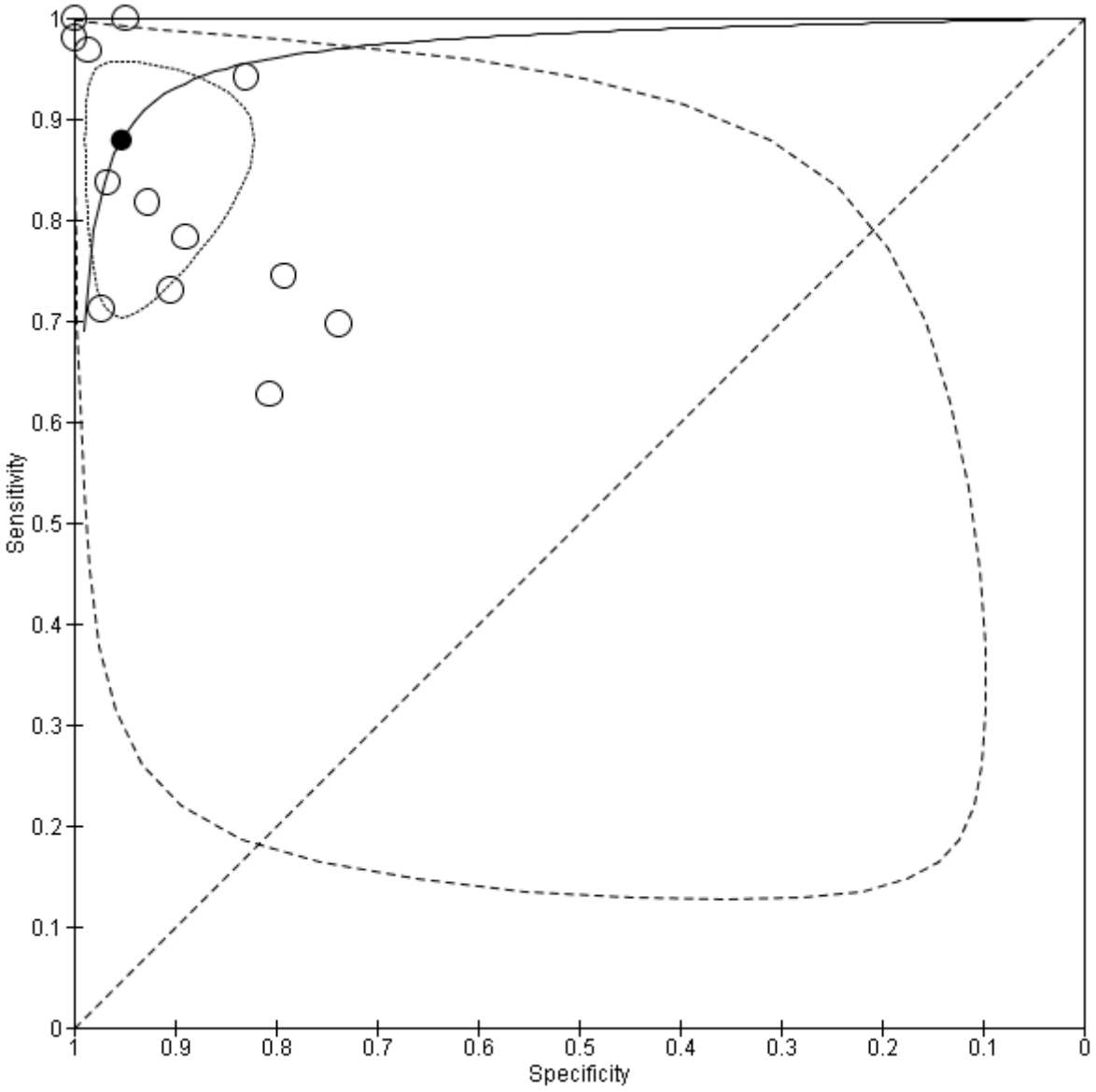


Figure 16: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+: per-person subgroup analysis by type of VFA scan

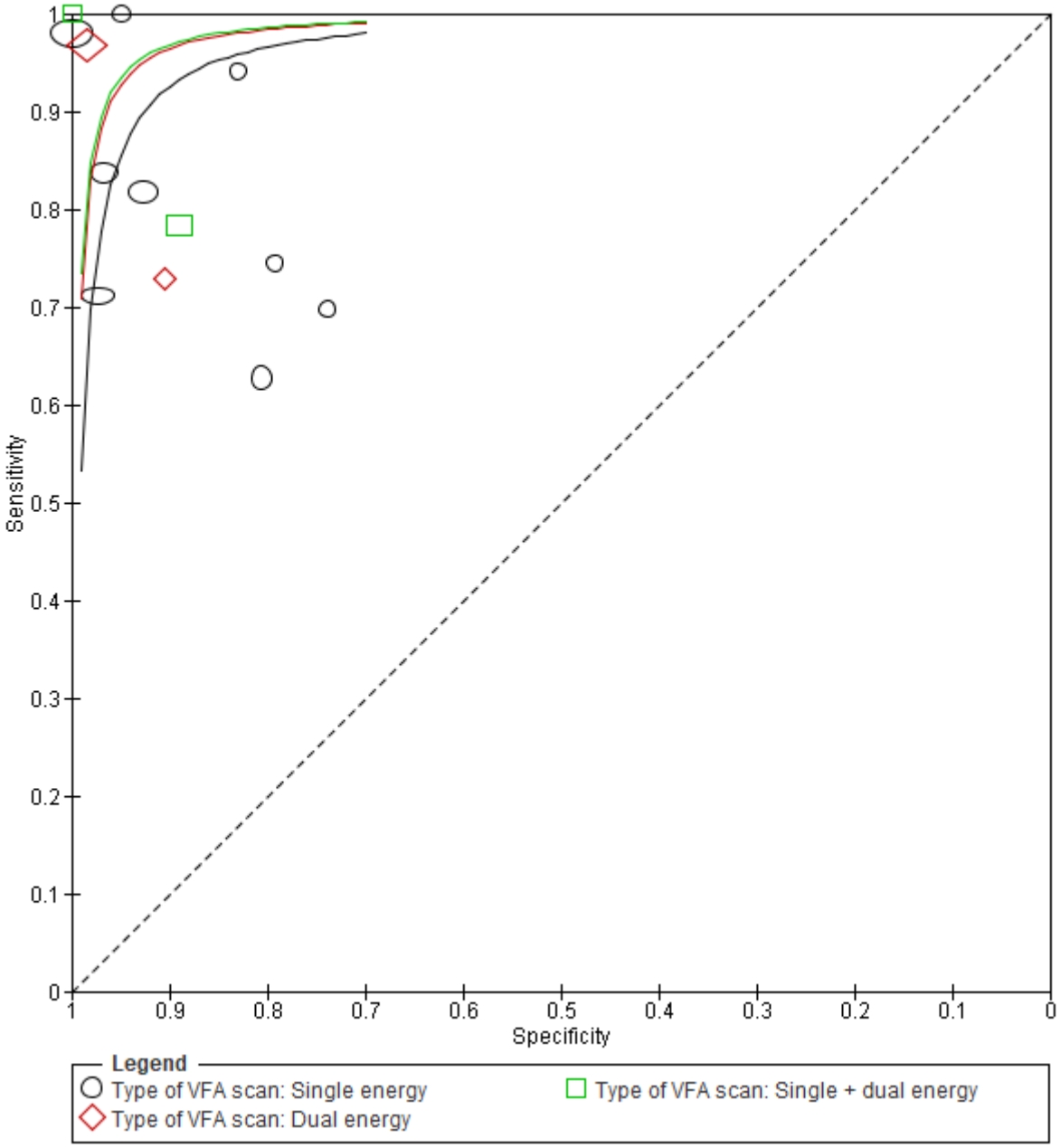
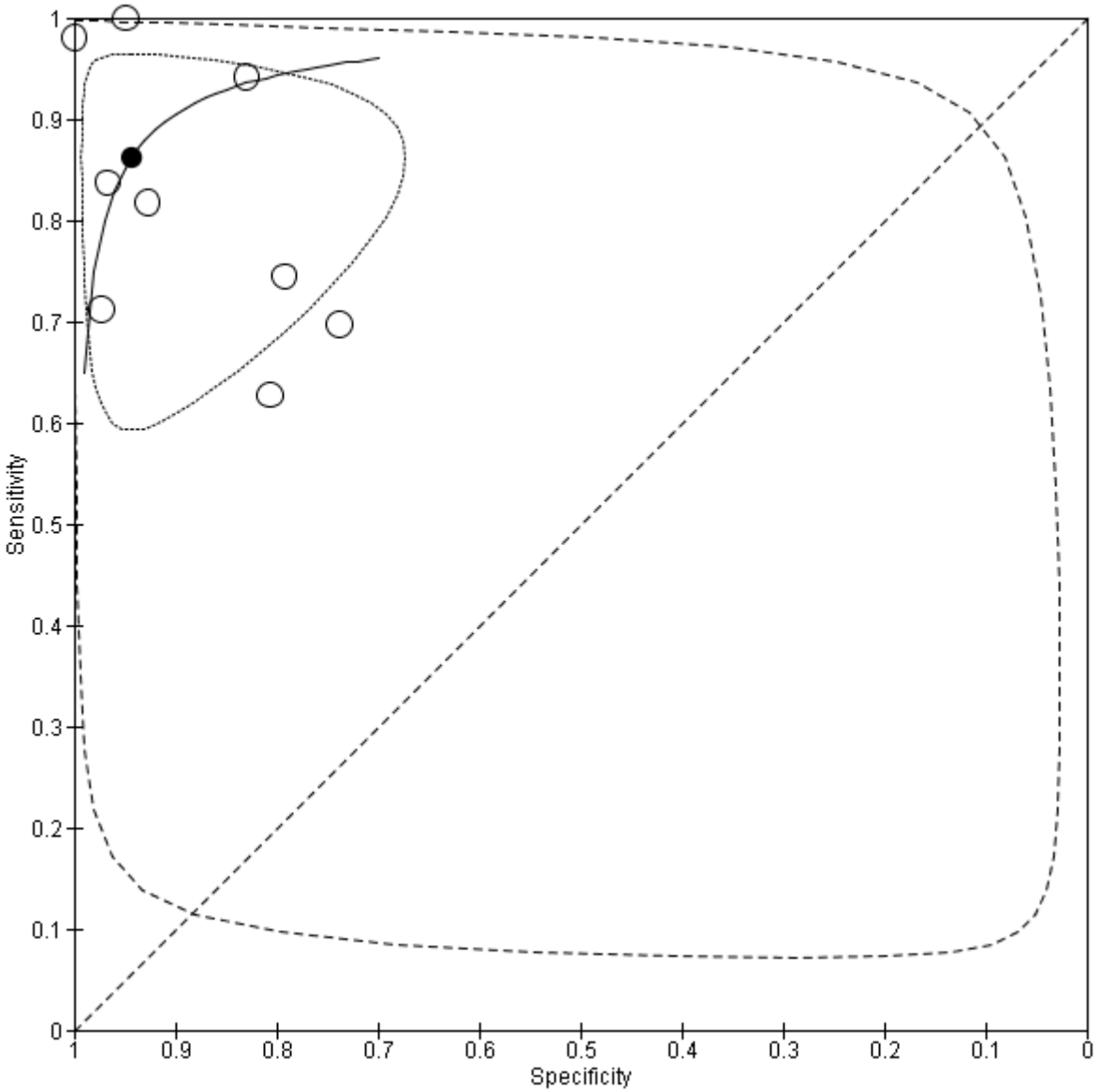


Figure 17: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 1+: per-person subgroup analysis: Single-energy VFA



Grade 2+ vertebral fractures

Figure 18: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+ - per-person analysis

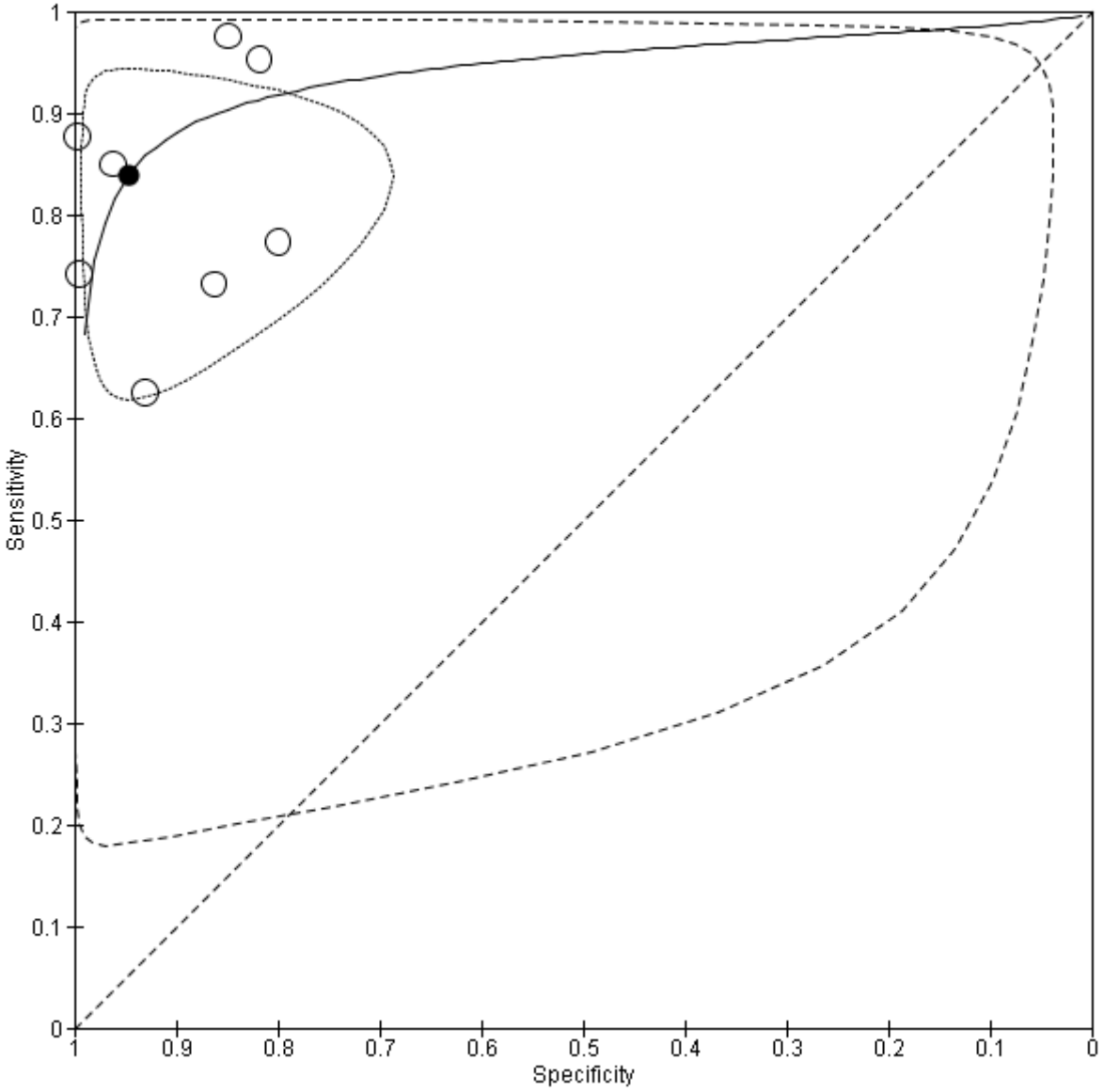


Figure 19: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+: per-person subgroup analysis by type of VFA scan

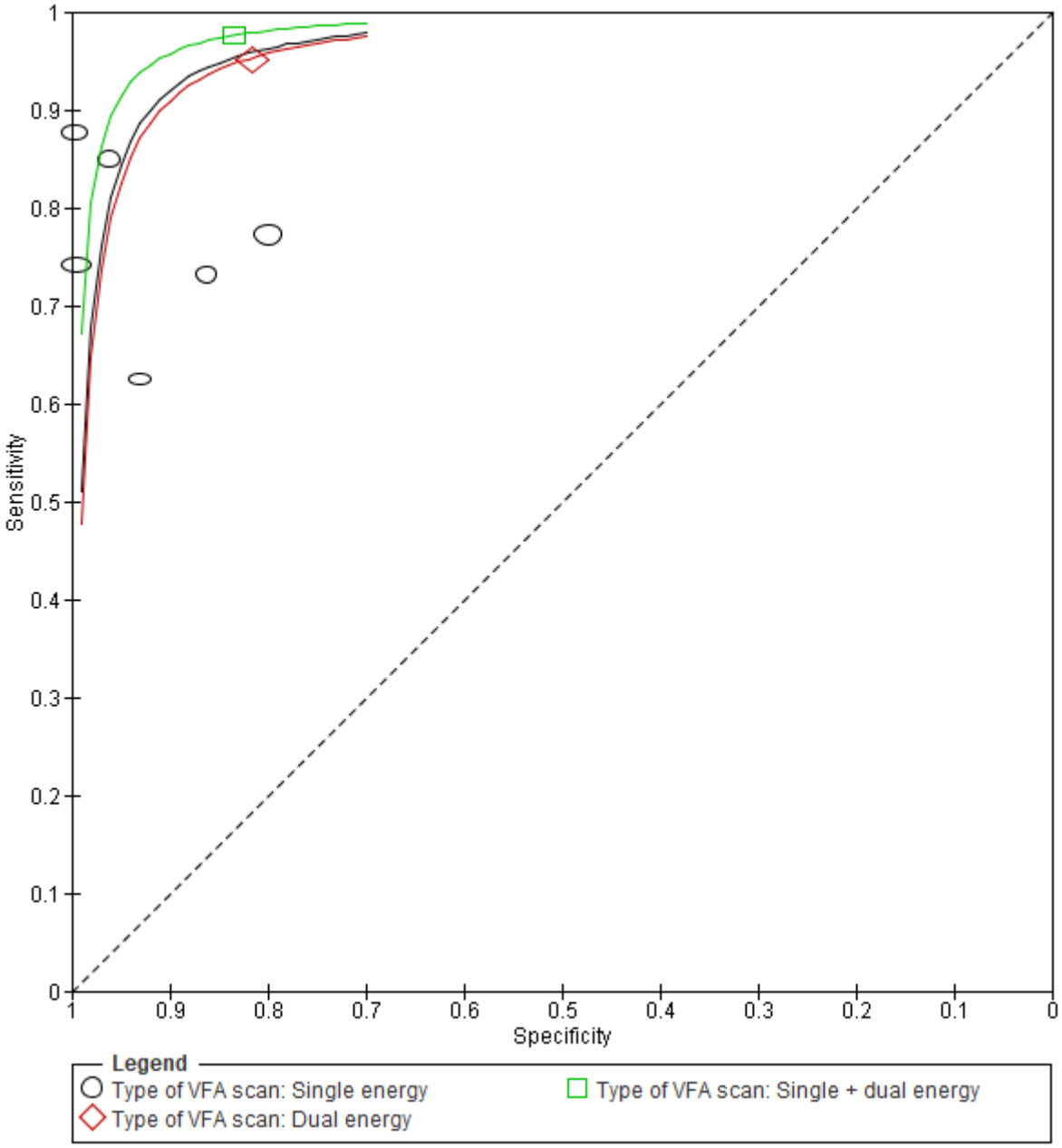
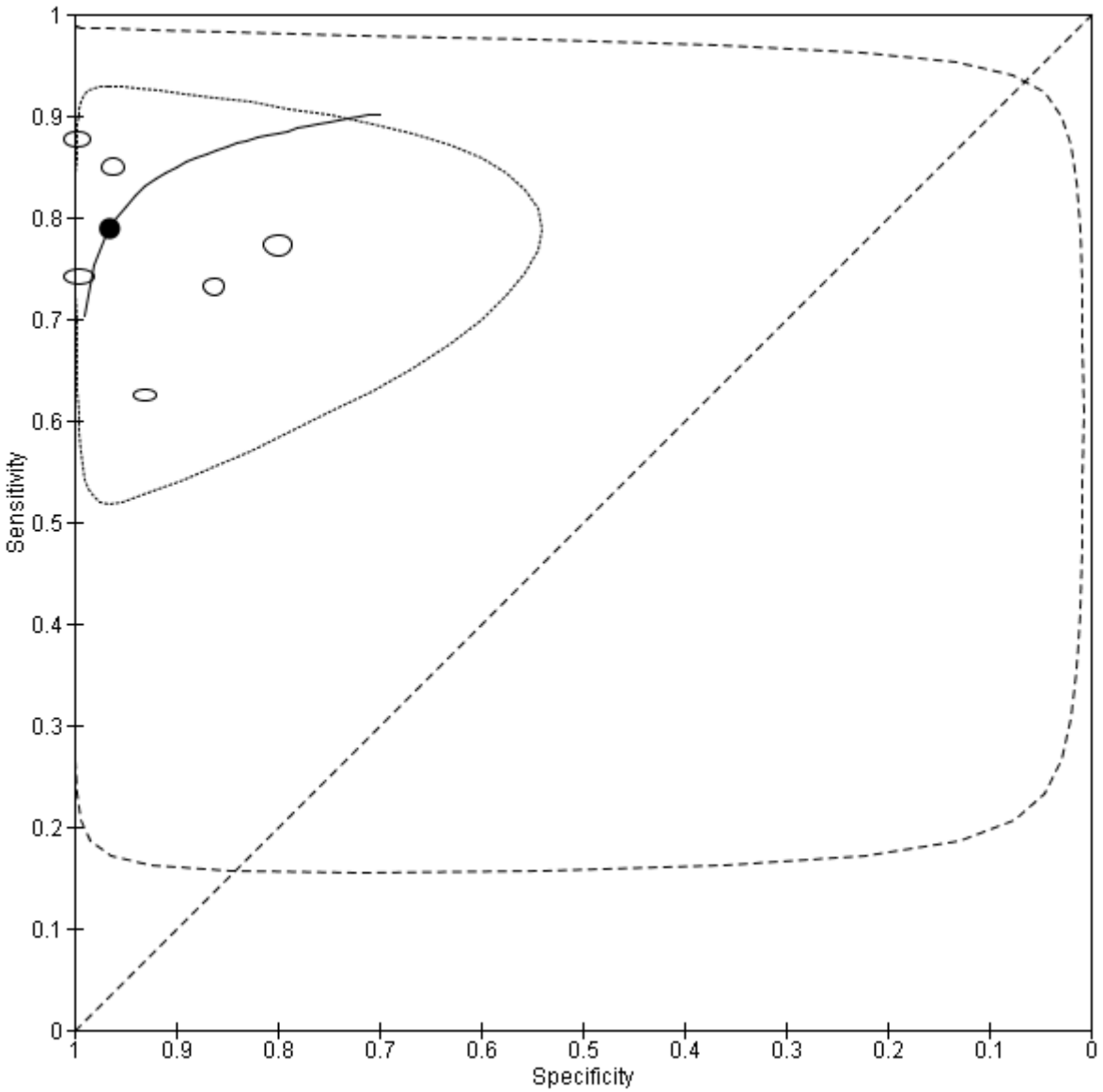


Figure 20: ROC plot of DXA with VFA compared to expert radiological assessment of conventional radiography for diagnosis of vertebral fracture Grade 2+: per-person subgroup analysis: Single-energy VFA



Appendix G GRADE QUADAS-2 assessments

Figure 21: Summary of QUADAS-2 risk of bias and applicability assessments

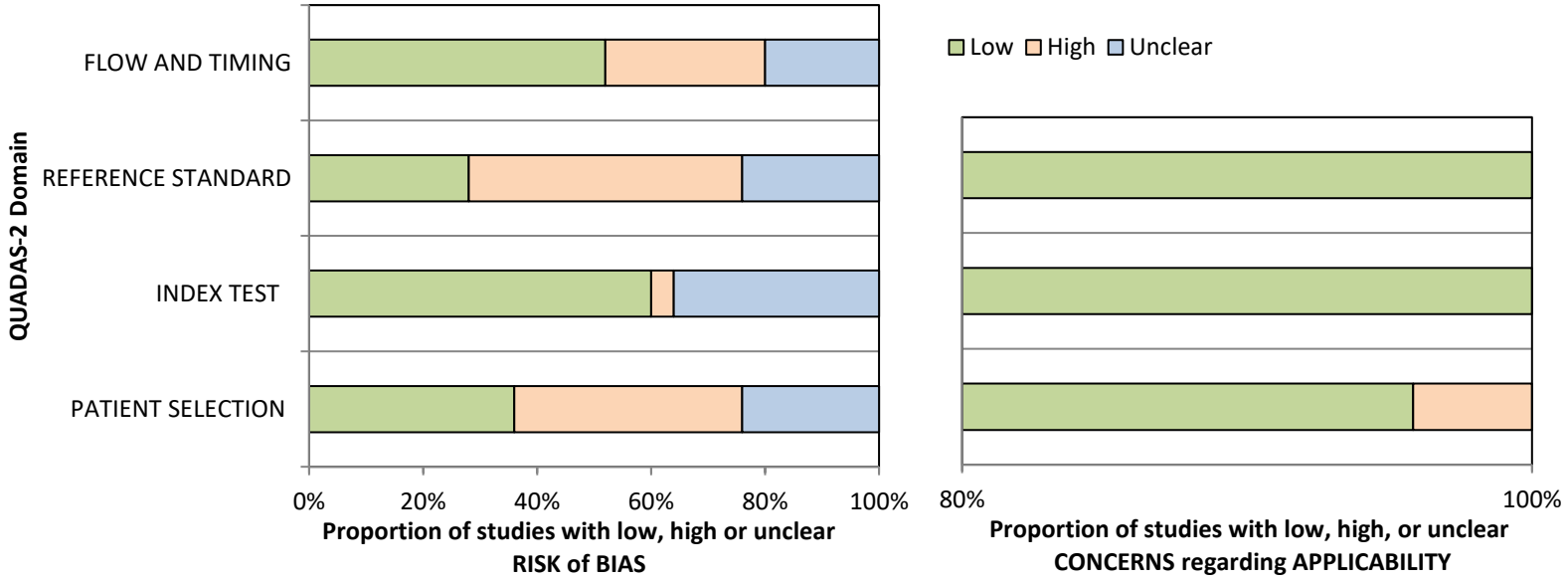


Table 12: QUADAS-2 assessments for included studies

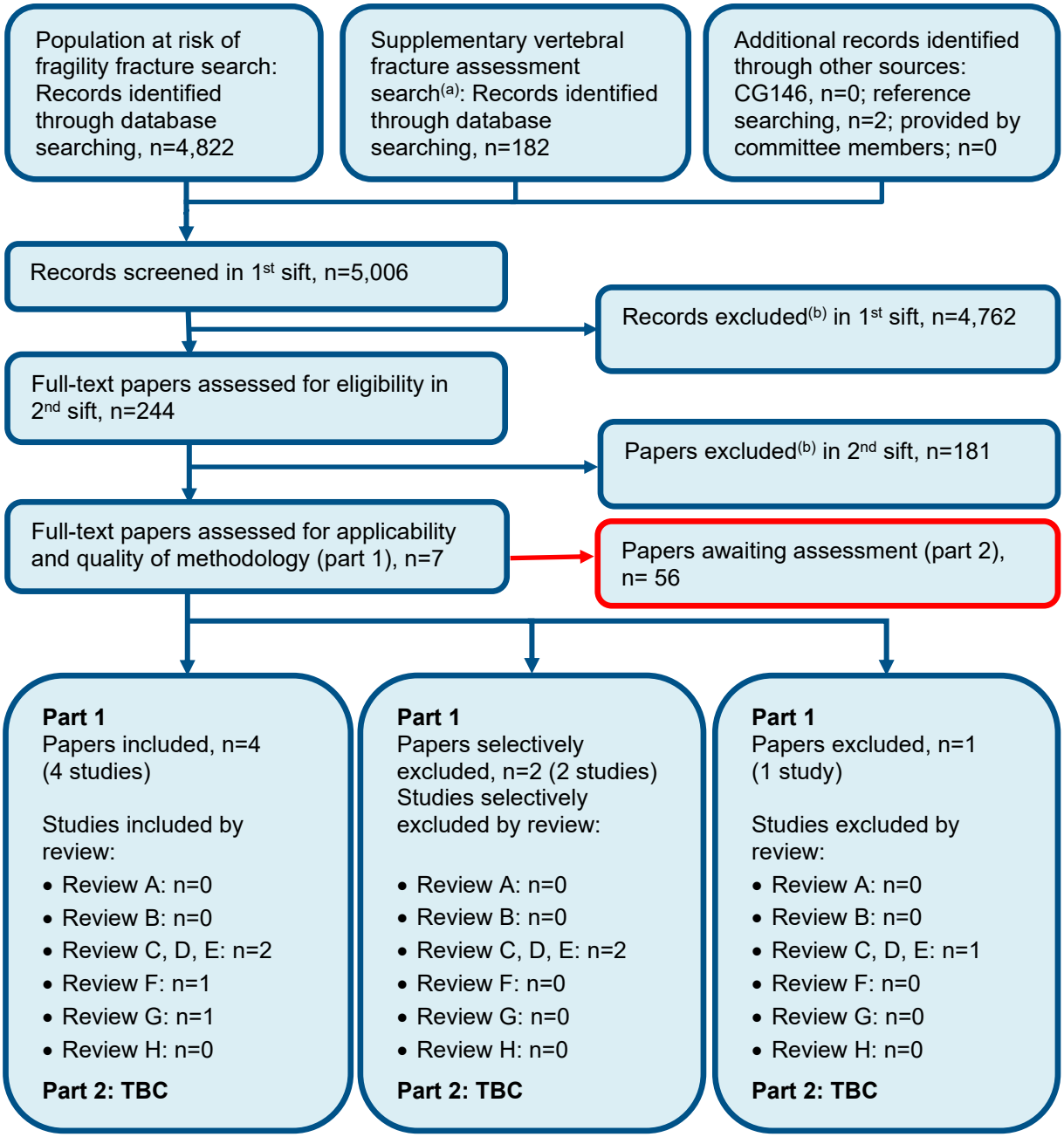
Study	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Bazzocchi 2012	Low	Unclear	Low	Low	Low	Low	Low
Binkley 2005	Unclear	Unclear	High	Low	Low	Low	Low
Chapurlat 2006	Low	Unclear	Unclear	Unclear	Low	Low	Low
Damiano 2006	Unclear	Unclear	High	High	Low	Low	Low
Deleskog 2016	High	Low	High	High	Low	Low	Low
Diacinti 2012A	High	Low	High	Low	Low	Low	Low
Diacinti 2012B	High	Low	High	Low	Low	Low	Low
Domiciano 2013	Unclear	Low	Low	Low	Low	Low	Low
Ferrar 2000 cohort	Low	Unclear	Unclear	High	Low	Low	Low
Ferrar 2000 cross sectional	Low	Unclear	Unclear	High	Low	Low	Low
Ferrar 2003	Low	Unclear	Unclear	Unclear	Low	Low	Low
Ferrar 2008 high risk	High	Low	High	Low	Low	Low	Low
Ferrar 2008 low risk	Low	Low	High	Low	Low	Low	Low
Fuerst 2009	Unclear	High	Low	Low	Low	Low	Low
Hospers 2009	High	Low	Low	Low	Low	Low	Low

Study	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Lee 2014	Low	Unclear	Unclear	Low	Low	Low	Low
Lin 2017	Low	Unclear	High	High	Low	Low	Low
Malgo 2017	High	Low	Unclear	Unclear	Low	Low	Low
Mazzaferro 2006	Unclear	Low	High	High	Low	Low	Low
Rea 2000B	High	Low	High	Low	Low	Low	Low
Rud 2016	Low	Low	Low	Low	Low	Low	Low
Schousboe 2006	High	Low	Low	Low	Low	Low	Low
Sullivan 2011	Unclear	Low	High	Unclear	Low	Low	Low
van Dort 2018	High	Low	High	High	Low	Low	Low
Vokes 2003	High	Low	Low	Unclear	Low	Low	Low

Appendix H Economic evidence study selection

Note that this guideline is being consulted on it two parts, but the health economic review search covered the full guideline. Only studies related to part 1 are included below. Studies that may be relevant to part 2 are noted but are not finalised.

Figure 22: Flow chart of health economic study selection for guideline



TBC= to be checked. These review questions will form the second instalment of this guideline update.

(a) Supplementary search for review questions F and G. Search methods in Appendix B of relevant evidence reports.
(b) Non-relevant population, intervention, comparison, design or setting; non-English language.

Appendix I Economic evidence tables

Study	Clark 2014			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALY) **Study design:** Deterministic decision analytic model **Approach to analysis:** Decision tree capturing the additional number of people treated as a result of VFA. Fractures avoided and GI adverse effects were incorporated. **Perspective:** UK NHS **Time horizon:** 5 years **Discounting:** Costs: NR; Outcomes: NR	**Population:** Fracture cohort: Women over 50 years attending for DXA after a low trauma fracture as part of FLS Primary care cohort: Women from primary care aged 65-80 years identified as being at high risk of having had a vertebral fracture[(a)] **Cohort settings:** Start age: 61.6 years **Scenarios:** NOGG pathway (treatment based on age-dependent FRAX risk thresholds in NOGG guideline) 20/3 pathway (treatment if FRAX risk of MOF 20% or hip fracture 3%) **Intervention 1:**	**Fracture cohort:** Total costs (mean per patient): Scenario 1 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR Scenario 2 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR) **Primary care cohort:** Total costs (mean per patient): Scenario 1 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR Scenario 2 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR)	**Fracture cohort** QALYs (mean per patient): Scenario 1 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR Scenario 2 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR) **Primary care cohort** Total costs (mean per patient): Scenario 1 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR Scenario 2 Intervention 1: NR Intervention 2: NR Incremental (2−1): NR (95% CI: NR; p=NR)	Authors 'best estimate' results with medication costs assuming most are on calcium/vitamin D supplements already, reduced cost of VFA (£15) assuming increased use of modern scanners and poor adherence resulting in only 17.5 % fracture reduction over 5 years. **Fracture cohort** Scenario 1 ICER (Intervention 2 versus Intervention 1): £2,130 per QALY gained Scenario 2 ICER (Intervention 2 versus Intervention 1): £3,243 per QALY gained **Primary care cohort** Scenario 1 ICER (Intervention 2 versus Intervention 1): £7,831 per QALY gained Scenario 2 ICER (Intervention 2 versus Intervention 1): Cost saving (assumed to also have higher QALYs).

	No VFA (treatment based on FRAX risk) **Intervention 2:** VFA (treatment based on FRAX risk plus treatment in those with vertebral fracture who were not otherwise Vertebral fractures were identified using six-point QM with the Spine Analyzer 3.2 software with a ≥25% reduction in height used to identity vertebral fractures.	**Currency & cost year:** 2011 UK pounds Cost components incorporated: Cost of VFA, medication costs (alendronate plus calcium and vitamin D), treatment-related adverse event costs. Fracture costs varied by fracture type and included length of inpatient stay, surgery, physiotherapy, and outpatient follow-up.		**Analysis of uncertainty:** Altering how vertebral fracture was identified using scenario 2 resulted in the following ICERs: 30% height reduction rule applied Fracture cohort: £150,222 per QALY gained Primary care cohort: £64,371 per QALY gained 25% height reduction plus lower fracture risk[(d)] rule applied Fracture cohort: £15,180 per QALY gained Primary care cohort: £20,843 per QALY gained ABQ rule applied Fracture cohort: £150,222 per QALY gained Primary care cohort: £92,912 per QALY gained In one-way sensitivity analysis for scenario 2, reducing treatment effectiveness from 35% to 17.5%, along with lowering the 5-year future fracture risk for untreated women from 35% to 25%, led to intervention 2 no longer being cost-effective compared to intervention 1.
Data sources				
Health outcomes: Change in clinical management as a result of VFA was informed by UK cohort analyses reported in the same paper. The fracture cohort consisted of patients from the Bristol area between 2008-2010 referred for DXA (n=377). The primary care cohort consistent of people identified as at high risk of vertebral fracture as part of an RCT that had DXA (n=251). All people had VFA at the time of DXA. Current management was estimated by				

calculating FRAX risk using height and weight recorded at the time of DXA with other risk factors collected via self-completed questionnaires (missing risk data was imputed) and applying risk-based treatment rules. Change in clinical management following VFA was defined as a vertebral fracture in a patient who would not otherwise be treated based to their fracture risk. Future fracture risk in additional people identified for treatment by VFA was taken from a study of 820 residents from Minnesota USA with prevalent vertebral fracture with an average follow-up period of around 5 years. Proportions of hip, forearm, humerus, or vertebral fractures were taken from a FLS in Glasgow over an 8-year period. The clinical effectiveness of alendronate in reducing fracture outcomes was based on an RCT. Persistence to treatment was taken from observational data of postmenopausal women in the UK from the GPRD. **Quality-of-life weights:** Baseline utilities: EQ-5D-3L with US general population tariff. Disutilities for fractures: tool/tariff unclear - were taken from a published systematic review with 16 studies, 11 of which used EQ-5D-3L with population tariff not reported. **Cost sources:** Additional cost of VFA was based on reimbursement costs by Medicare in the USA (£24) but reduced to £15 in 'best estimate' analysis to reflect expected lower cost due to advanced scanners where patients do not need to be repositioned). Costs of medication were taken from BNF. Fracture-related costs were taken from UK data where possible otherwise Swedish data where this were not available. The cost of managing treatment-related adverse events taken from a published paper following up patients with osteoporosis fracture over 8 years in a Glasgow FLS setting.
Comments
Source of funding: None declared. **Limitations:** 2011 cost year and VFA costs informed by US Medicare costs may not reflect current NHS context. It is not stated whether costs and health outcomes were appropriately discounted over the model time horizon. Utilities methods fully aligned with NICE reference case. Decision tree may not be the most appropriate model structure for osteoporosis. Time horizon of 5 years is not sufficiently long to capture lifetime effects of outcomes such as fracture. Some relevant costs may be omitted e.g. residential care. Effectiveness of intervention under consideration estimated based on a retrospective cohort. Neither total nor incremental costs and QALYs were reported, only ICERs. Probabilistic analysis was not undertaken. **Other:** n/a
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; ABQ= algorithm-based qualitative assessment of vertebral fracture; CUA= cost–utility analysis; da= deterministic analysis; DXA= dual-energy X-ray absorptiometry; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); FLS= fracture liaison service; GPRD= general practice research database; ICER= incremental cost-effectiveness ratio; n/a= not applicable; NR= not reported; NOGG= National Osteoporosis Guideline Group; QALYs= quality-adjusted life years; RCT= randomised controlled trial; VFA= vertebral fracture assessment

(a) Identified as being at high risk of having had a vertebral fracture using the COSHIBA screening tool that incorporated assessment of four clinical risk factors: height loss, history of previous non-vertebral fracture, Margolis back pain score, and rib-to-pelvis distance.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

(d) 25% future fracture risk over 5 years instead of 35%

Appendix J Health economic model

No original economic modelling was undertaken for this review question.

Appendix K Excluded studies

K.1 Diagnostic and clinical evidence

Table 13: Excluded studies

Study	Reason for exclusion
Abe, Kiyoko, Tamaki, Junko, Kadowaki, Eiko et al. (2008) Use of anthropometric indicators in screening for undiagnosed vertebral fractures: a cross-sectional analysis of the Fukui Osteoporosis Cohort (FOC) study. BMC musculoskeletal disorders 9: 157	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Bazzocchi, Alberto, Diano, Danila, Battista, Giuseppe et al. (2012) New dual-energy X-ray absorptiometry equipment in the assessment of vertebral fractures: technical limits and software accuracy. Skeletal radiology 41(7): 823-9	- Reference standard is not listed in review protocol
Bergot, C, Laval-Jeantet, A M, Hutchinson, K et al. (2001) A comparison of spinal quantitative computed tomography with dual energy X-ray absorptiometry in European women with vertebral and nonvertebral fractures. Calcified tissue international 68(2): 74-82	- Study does not contain an intervention relevant to this review protocol Study compares DXA only without VFA
Boehm, Elena, Kraft, Eduard, Biebl, Johanna Theresia et al. (2024) Quantitative computed tomography has higher sensitivity detecting critical bone mineral density compared to dual-energy X-ray absorptiometry in postmenopausal women and elderly men with osteoporotic fractures: a real-life study. Archives of orthopaedic and trauma surgery 144(1): 179-188	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Briot, K, Fechtenbaum, J, Etcheto, A et al. (2015) Diagnosis of vertebral fractures using a low-dose biplanar imaging system. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 26(11): 2649-55	- Reference standard is not listed in review protocol

Study	Reason for exclusion
Buehring, B, Krueger, D, Checovich, M et al. (2010) Vertebral fracture assessment: impact of instrument and reader. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 21(3): 487-94	- Reference standard is not listed in review protocol
Carberry, George A, Pooler, B Dustin, Binkley, Neil et al. (2013) Unreported vertebral body compression fractures at abdominal multidetector CT. Radiology 268(1): 120-6	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Chen, Peiqi, Miller, Paul D, Binkley, Neil C et al. (2008) Use of lowest single lumbar spine vertebra bone mineral density T-score and other T-score approaches for diagnosing osteoporosis and relationships with vertebral fracture status. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 11(4): 525-31	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Chen, Rong, Liu, Shuying, Huang, Meng et al. (2021) Comparison of the NOF and NOGG guidelines for spinal radiographic examination in postmenopausal Chinese women. Archives of osteoporosis 16(1): 5	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Choi, Y J, Yang, S-O, Shin, C S et al. (2012) The importance of morphometric radiographic vertebral assessment for the detection of patients who need pharmacological treatment of osteoporosis among postmenopausal diabetic Korean women. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 23(8): 2099-2105	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Chou, Sharon H, Vokes, Tamara J, Ma, Siu-Ling et al. (2014) Simplified criteria for selecting patients for vertebral fracture assessment. Journal of clinical	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
densitometry : the official journal of the International Society for Clinical Densitometry 17(3): 386-91	
de Klerk, G, Hegeman, J H, Bronkhorst, P et al. (2012) The (a)-Symptomatic Vertebral Fracture: A Frequently Discovered Entity With Clinical Relevance in Fracture Patients Screened on Osteoporosis. Geriatric orthopaedic surgery & rehabilitation 3(2): 74-8	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Difede, G, Scalzo, G, Bucchieri, S et al. (2010) Underreported vertebral fractures in an Italian population: comparison of plain radiographs vs quantitative measurements. La Radiologia medica 115(7): 1101-10	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
El Maghraoui, Abdellah, Sadni, Siham, Jbili, Nabil et al. (2014) The discriminative ability of FRAX, the WHO algorithm, to identify women with prevalent asymptomatic vertebral fractures: a cross-sectional study. BMC musculoskeletal disorders 15: 365	- Reference standard is not listed in review protocol
Ferrar, L; Jiang, G; Eastell, R (2001) Vertebral wedge angle measured by morphometric X-ray absorptiometry. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 12(11): 914-21	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Florez, Helena, Hernandez-Rodriguez, Jose, Muxi, Africa et al. (2020) Trabecular bone score improves fracture risk assessment in glucocorticoid-induced osteoporosis. Rheumatology (Oxford, England) 59(7): 1574-1580	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Formica, C A, Nieves, J W, Cosman, F et al. (1998) Comparative assessment of bone mineral measurements using dual X-ray absorptiometry and peripheral quantitative computed tomography. Osteoporosis international : a journal established as result of cooperation between the European	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 8(5): 460-7	
Ginther, Jay P; Ginther, Ann W; Brodersen, Lisa D (2017) ADDING VFA TO DXA IDENTIFIES FRACTURE RISK IN A WAY NOT DUPLICATED BY OTHER MEASURES. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 23(12): 1375-1378	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Greenspan, S L, von Stetten, E, Emond, S K et al. (2001) Instant vertebral assessment: a noninvasive dual X-ray absorptiometry technique to avoid misclassification and clinical mismanagement of osteoporosis. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 4(4): 373-80	- Reference standard is not listed in review protocol
Greenspan, Susan L, Perera, Subashan, Nace, David et al. (2012) FRAX or fiction: determining optimal screening strategies for treatment of osteoporosis in residents in long-term care facilities. Journal of the American Geriatrics Society 60(4): 684-90	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Guo, SiJia, An, Ning, Lin, JiSheng et al. (2022) Comparison of four tools to identify painful new osteoporotic vertebral fractures in the postmenopausal population in Beijing. Frontiers in endocrinology 13: 1013755	- Reference standard is not listed in review protocol
Hedderich, D.M., Maegerlein, C., Baum, T. et al. (2019) Differentiation of Acute/Subacute versus Old Vertebral Fractures in Multislice Detector Computed Tomography: Is Magnetic Resonance Imaging Always Needed?. World Neurosurgery 122: e676-e683	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Iimori, Soichiro, Mori, Yoshihiro, Akita, Wataru et al. (2012) Diagnostic usefulness of bone mineral density and biochemical	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
markers of bone turnover in predicting fracture in CKD stage 5D patients--a single-center cohort study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 27(1): 345-51	
Ilic Stojanovic, O, Vuceljic, M, Lazovic, M et al. (2017) Bone mineral density at different sites and vertebral fractures in Serbian postmenopausal women. Climacteric : the journal of the International Menopause Society 20(1): 37-43	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Ishizu, Hotaka, Shimizu, Tomohiro, Sakamoto, Yuki et al. (2024) Radiofrequency Echographic Multispectrometry (REMS) can Overcome the Effects of Structural Internal Artifacts and Evaluate Bone Fragility Accurately. Calcified tissue international 114(3): 246-254	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Ito, M, Hayashi, K, Ishida, Y et al. (1997) Discrimination of spinal fracture with various bone mineral measurements. Calcified tissue international 60(1): 11-5	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Jacobs-Kosmin, Dana, Sandorfi, Nora, Murray, Heather et al. (2005) Vertebral deformities identified by vertebral fracture assessment: associations with clinical characteristics and bone mineral density. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 8(3): 267-72	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Jager, P L, Jonkman, S, Koolhaas, W et al. (2011) Combined vertebral fracture assessment and bone mineral density measurement: a new standard in the diagnosis of osteoporosis in academic populations. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 22(4): 1059-68	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
Jamal, S A; West, S L; Nickolas, T L (2014) The clinical utility of FRAX to discriminate fracture status in men and women with chronic kidney disease. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 25(1): 71-6	- Reference standard is not listed in review protocol
Jergas, M, Breitenseher, M, Gluer, C C et al. (1995) Which vertebrae should be assessed using lateral dual-energy X-ray absorptiometry of the lumbar spine. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 5(3): 196-204	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Jergas, M and Genant, H K (1997) Spinal and femoral DXA for the assessment of spinal osteoporosis. Calcified tissue international 61(5): 351-7	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Johannesdottir, Fjola; Allaire, Brett; Bouxsein, Mary L (2018) Fracture Prediction by Computed Tomography and Finite Element Analysis: Current and Future Perspectives. Current osteoporosis reports 16(4): 411-422	- Review article but not a systematic review
Kaji, Hiroshi, Yamauchi, Mika, Chihara, Kazuo et al. (2005) The threshold of bone mineral density for vertebral fractures in female patients with primary hyperparathyroidism. European journal of endocrinology 153(3): 373-8	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Kalvesten, Johan, Lui, Li-Yung, Brismar, Torkel et al. (2016) Digital X-ray radiogrammetry in the study of osteoporotic fractures: Comparison to dual energy X-ray absorptiometry and FRAX. Bone 86: 30-5	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
Kim, Hyoun-Ah, Lee, Hyun Young, Jung, Ju-Yang et al. (2020) Trabecular Bone Score Is a Useful Parameter for the Prediction of Vertebral Fractures in Patients With Polymyalgia Rheumatica. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 23(3): 373-380	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Kim, Y W, Kim, J H, Yoon, S H et al. (2017) Vertebral bone attenuation on low-dose chest CT: quantitative volumetric analysis for bone fragility assessment. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 28(1): 329-338	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Kroger, H, Lunt, M, Reeve, J et al. (1999) Bone density reduction in various measurement sites in men and women with osteoporotic fractures of spine and hip: the European quantitation of osteoporosis study. Calcified tissue international 64(3): 191-9	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Kuet, K-P; Charlesworth, D; Peel, N F A (2013) Vertebral fracture assessment scans enhance targeting of investigations and treatment within a fracture risk assessment pathway. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 24(3): 1007-14	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lai, Ee-Ling, Huang, Wen-Nan, Chen, Hsin-Hua et al. (2020) Degraded microarchitecture by low trabecular bone score is associated with prevalent vertebral fractures in patients with systemic lupus erythematosus. Archives of osteoporosis 15(1): 54	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Laib, A, Newitt, D C, Lu, Y et al. (2002) New model-independent measures of trabecular bone structure applied to in vivo high-	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
resolution MR images. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 13(2): 130-6	
Lajlev, Siv E; Rejnmark, Lars; Harslof, Torben (2019) T-score differences and nonprogression in lumbar vertebrae as predictors of vertebral fractures. Clinical endocrinology 91(1): 58-62	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lamy, O., Krieg, M.-A., Stoll, D. et al. (2012) The OsteoLaus Cohort Study: Bone mineral density, micro-architecture score and vertebral fracture assessment extracted from a single DXA device in combination with clinical risk factors improve significantly the identification of women at high risk of fracture. Osteologie 21(2): 77-82	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lang, T F, Li, J, Harris, S T et al. (1999) Assessment of vertebral bone mineral density using volumetric quantitative CT. Journal of computer assisted tomography 23(1): 130-7	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lee, Byung-Jou, Koo, Hae-Won, Yoon, Sang Won et al. (2021) Usefulness of Trabecular CT Attenuation Measurement of Lumbar Spine in Predicting Osteoporotic Compression Fracture: Is the L4 Trabecular Region of Interest Most Relevant?. Spine 46(3): 175-183	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lee, J-H, Lee, Y K, Oh, S-H et al. (2016) A systematic review of diagnostic accuracy of vertebral fracture assessment (VFA) in postmenopausal women and elderly men. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 27(5): 1691-9	- Systematic review used as source of primary studies
Lee, Kyung-Ann; Kim, Hyun-Joo; Kim, Hyun-Sook (2023) Comparison of predictive value of FRAX, trabecular bone score, and	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
bone mineral density for vertebral fractures in systemic sclerosis: A cross-sectional study. Medicine 102(2): e32580	
Lee, S J, Binkley, N, Lubner, M G et al. (2016) Opportunistic screening for osteoporosis using the sagittal reconstruction from routine abdominal CT for combined assessment of vertebral fractures and density. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 27(3): 1131-1136	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lems, W F, Paccou, J, Zhang, J et al. (2021) Vertebral fracture: epidemiology, impact, and use of DXA vertebral fracture assessment in fracture liaison services. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 32(3): 399-411	- Review article but not a systematic review
Lewiecki, E Michael and Laster, Andrew J (2006) Clinical review: Clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry. The Journal of clinical endocrinology and metabolism 91(11): 4215-22	- Review article but not a systematic review
Li, Caixia, Gluer, Claus-C, Eastell, Richard et al. (2012) Tree-structured subgroup analysis of receiver operating characteristic curves for diagnostic tests. Academic radiology 19(12): 1529-36	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Li, Na, Li, Xin-Min, Xu, Li et al. (2013) Comparison of QCT and DXA: Osteoporosis Detection Rates in Postmenopausal Women. International journal of endocrinology 2013: 895474	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lin, Wentao, He, Chaoqin, Xie, Faqin et al. (2023) Discordance in lumbar bone mineral density measurements by quantitative	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
computed tomography and dual-energy X-ray absorptiometry in postmenopausal women: a prospective comparative study. The spine journal : official journal of the North American Spine Society 23(2): 295-304	
Lin, Wentao, He, Chaoqin, Xie, Faqin et al. (2023) Quantitative CT screening improved lumbar BMD evaluation in older patients compared to dual-energy X-ray absorptiometry. BMC geriatrics 23(1): 231	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Lin, Wentao, He, Chaoqin, Xie, Faqin et al. (2023) Assessment of bone density using the 1.5 T or 3.0 T MRI-based vertebral bone quality score in older patients undergoing spine surgery: does field strength matter?. The spine journal : official journal of the North American Spine Society 23(8): 1172-1181	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Loffler, Maximilian T, Jacob, Alina, Valentinitsch, Alexander et al. (2019) Improved prediction of incident vertebral fractures using opportunistic QCT compared to DXA. European radiology 29(9): 4980-4989	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Muschitz, C., Dimai, H.P., Kocijan, R. et al. (2013) The discriminatory capacity of BMD measurements by DXL at the calcaneus and DXA at the hip and spine including clinical risk factors to detecting patients with vertebral fractures. Journal fur Mineralstoffwechsel 20(2): 52-56	- Duplicate reference
Muschitz, C, Dimai, H P, Kocijan, R et al. (2013) The discriminatory capacity of BMD measurements by DXA and dual X-ray and laser (DXL) at the calcaneus including clinical risk factors for detecting patients with vertebral fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 24(8): 2181-90	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
Nassar, K, Paternotte, S, Kolta, S et al. (2014) Added value of trabecular bone score over bone mineral density for identification of vertebral fractures in patients with areal bone mineral density in the non-osteoporotic range. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 25(1): 243-9	- Reference standard is not listed in review protocol
Nishiyama, K K, Macdonald, H M, Hanley, D A et al. (2013) Women with previous fragility fractures can be classified based on bone microarchitecture and finite element analysis measured with HR-pQCT. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 24(5): 1733-40	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Osella, Giangiacomo, Priola, Adriano Massimiliano, Priola, Sandro Massimo et al. (2018) Dual-Energy X-ray Absorptiometry Predictors of Vertebral Deformities in Beta-Thalassemia Major. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 21(4): 507-516	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Patel, Nikita, Dahl, Katrina, O'Rourke, Rachael et al. (2023) Vertebral CT attenuation outperforms standard clinical fracture risk prediction tools in detecting osteoporotic disease in lung cancer screening participants. The British journal of radiology 96(1151): 20220992	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Pavlov, Lialia; Gamble, Gregory D; Reid, Ian R (2005) Comparison of dual-energy X-ray absorptiometry and conventional radiography for the detection of vertebral fractures. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 8(4): 379-85	- Data not reported in an extractable format or a format that can be analysed

Study	Reason for exclusion
Poullain, Francois, Champsaur, Pierre, Pauly, Vanessa et al. (2023) Vertebral trabecular bone texture analysis in opportunistic MRI and CT scan can distinguish patients with and without osteoporotic vertebral fracture: A preliminary study. European journal of radiology 158: 110642	- Data not reported in an extractable format or a format that can be analysed
Pulkkinen, P., Saarakkala, S., Nieminen, M.T. et al. (2013) Standard Radiography: Untapped Potential in the Assessment of Osteoporotic Fracture Risk. European Radiology 23(5): 1375-1382	- Review article but not a systematic review
Rea, J A, Chen, M B, Li, J et al. (2000A) Morphometric X-ray absorptiometry and morphometric radiography of the spine: a comparison of prevalent vertebral deformity identification. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 15(3): 564-74	- Reference standard is not listed in review protocol Compares Eastell and McCloskey quantitative algorithms
Rea, J A, Chen, M B, Li, J et al. (1999) Morphometric X-ray absorptiometry and morphometric radiography of the spine: a comparison of analysis precision in normal and osteoporotic subjects. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 9(6): 536-44	- Data not reported in an extractable format or a format that can be analysed
Roberts, Martin, Cootes, Tim, Pacheco, Elisa et al. (2007) Quantitative vertebral fracture detection on DXA images using shape and appearance models. Academic radiology 14(10): 1166-78	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Santos, Livia Marcela Dos, Ohe, Monique Nakayama, Pallone, Sthefanie Giovanna et al. (2021) Trabecular Bone Score (TBS) in Primary Hyperparathyroidism (PHPT): A Useful Tool?. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 24(4): 563-570	- Reference standard is not listed in review protocol

Study	Reason for exclusion
Shetty, Sahana, John, Bimi, Mohan, Sofia et al. (2020) Vertebral fracture assessment by dual-energy X-ray absorptiometry along with bone mineral density in the evaluation of postmenopausal osteoporosis. Archives of osteoporosis 15(1): 25	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Stephens, Kelly I, Rubinsztain, Leon, Payan, John et al. (2016) DUAL-ENERGY X-RAY ABSORPTIOMETRY AND CALCULATED FRAX RISK SCORES MAY UNDERESTIMATE OSTEOPOROTIC FRACTURE RISK IN VITAMIN D-DEFICIENT VETERANS WITH HIV INFECTION. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 22(4): 440-6	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
van den Berg, Martha, Verdijk, Noortje A, van den Bergh, Joop P W et al. (2011) Vertebral fractures in women aged 50 years and older with clinical risk factors for fractures in primary care. Maturitas 70(1): 74-9	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Viswanathan, Meera, Reddy, Shivani, Berkman, Nancy et al. (2018) Screening to Prevent Osteoporotic Fractures: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 319(24): 2532-2551	- Systematic review not used as a source of primary studies
Vosse, D, Heijckmann, C, Landewe, R et al. (2007) Comparing morphometric X-ray absorptiometry and radiography in defining vertebral wedge fractures in patients with ankylosing spondylitis. Rheumatology (Oxford, England) 46(11): 1667-71	- Study does not report sufficient information to determine assessment methods
Xu, Xiao-Ming, Li, Na, Li, Kai et al. (2019) Discordance in diagnosis of osteoporosis by quantitative computed tomography and dual-energy X-ray absorptiometry in Chinese elderly men. Journal of orthopaedic translation 18: 59-64	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

Study	Reason for exclusion
Yang, Hui, Yan, Sheng, Li, Jiang et al. (2022) Prediction of acute versus chronic osteoporotic vertebral fracture using radiomics-clinical model on CT. European journal of radiology 149: 110197	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Yin, Houjie, Lin, Wentao, Xie, Faqin et al. (2023) MRI-based Vertebral Bone Quality Score for Osteoporosis Screening Based on Different Osteoporotic Diagnostic Criteria Using DXA and QCT. Calcified tissue international 113(4): 383-392	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Yu, W, Gluer, C C, Grampp, S et al. (1995) Spinal bone mineral assessment in postmenopausal women: a comparison between dual X-ray absorptiometry and quantitative computed tomography. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 5(6): 433-9	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Zaia, Annamaria, Rossi, Roberto, Galeazzi, Roberta et al. (2021) Fractal lacunarity of trabecular bone in vertebral MRI to predict osteoporotic fracture risk in over-fifties women. The LOTO study. BMC musculoskeletal disorders 22(1): 108	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Zarzour, Fatima and Leslie, William D (2024) Fracture Risk Associated with Different Numbers and Combinations of Lumbar Vertebrae: The Manitoba BMD Registry. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 27(3): 101502	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture
Zhang, Bo, Zhou, Lu-Ping, Zhang, Xian-Liang et al. (2023) Which Indicator Among Lumbar Vertebral Hounsfield Unit, Vertebral Bone Quality, or Dual-Energy X-Ray Absorptiometry-Measured Bone Mineral Density Is More Efficacious in Predicting Thoracolumbar Fragility Fractures?. Neurospine 20(4): 1193-1204	- Study does not examine diagnostic accuracy of DXA with VFA to identify vertebral fracture

K.2 Health economic studies

If any published health economic studies relevant to this question met the inclusion criteria (relevant population, comparators, economic study design, published 2009 or later and not from non-OECD country or USA) but were excluded following appraisal of applicability and methodological quality they are listed below with reasons. See the health economic protocol for more details.

None.

Appendix L Recommendation for research

L.1 What is the diagnostic accuracy of DXA-based VFA scan for identifying vertebral fractures?

L.1.1 Why this is important

Vertebral fractures (VFs) are the most common form of 'fragility' fracture associated with osteoporosis, but many remain undetected. The identification of vertebral fractures and subsequent treatment would reduce people's risk of future fractures and associated morbidity and mortality. The use of DXA rather than X-ray to identify VFs will also reduce exposure to ionising radiation. This question is to determine the accuracy of the newer generation scanners which have increased image quality and resolution, which should result in higher discriminatory accuracy (sensitivity and specificity) for detecting vertebral fractures.

L.1.2 Rationale for the recommendation for research

Importance to 'patients' or the population	New evidence could support existing recommendation on DXA-based VFA scans and strengthen the recommendations. The identification of vertebral fractures and subsequent treatment would reduce people's risk of future fractures and associated morbidity and mortality. Use of DXA rather than X-ray to identify VFs will also reduce exposure to ionizing radiation.
Relevance to NICE guidance	High: the research is essential to inform future updates of key recommendations in the guidance.
Relevance to the NHS	The aim would be to identify people with vertebral fractures who may need treatment to reduce the risk of subsequent fractures.
National priorities	High relevance to the NICE guideline for Osteoporosis. Consistent with 10-year plan to move management into the community and focus on prevention.
Current evidence base	Most evidence on accuracy of DXA-based VFA scans uses older scanners (see Evidence review G) and shows low specificity. Recent scanners have increased image quality and resolution, which should result in higher discriminatory accuracy (sensitivity and specificity) for detecting vertebral fractures.
Equality considerations	None known

L.1.3 Modified PICO table

Population	Adults (18 years and older) who are having a DXA assessment.
Target condition	Vertebral fracture
Index test	DXA with vertebral fracture assessment (VFA) using newer generation scanners

Reference standard	Expert radiological assessment of X-ray, MRI, or CT
Statistical measures	Accuracy of estimation of vertebral fracture: • Sensitivity/ specificity • Positive and negative likelihood ratio • Area under the curve (AUC)
Study design	Diagnostic: cohort and cross-sectional studies
Timeframe	Medium term. Completed prior to future updates of the osteoporosis guideline to inform future recommendations.

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