**Region Västra Götaland, HTA-centrum**
Regional activity based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
HTA report 2019:104

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

# Trabecular bone pattern assessment in dental radiographs for prediction of bone fracture risk [Utvärdering av trabekulärt benmönster i tandröntgenbilder för prediktion av benfrakturrisk]

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Published January 2019
2019:104
Suggested citation: Johanen A, Bernhardsson S, Hagman J, Hakeberg M, Hange D, Jonasson G, Laine C, Liljegren A, Lund H, Persson C, Svensson M, Stadig I, Svensson M, Wartenberg C, Sjögren P.
Trabecular bone pattern assessment in dental radiographs for prediction of fracture risk [Utvärdering av trabekulärt benmönster i tandröntgenbilder för prediktion av frakturrisk]. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2019. Regional activity based HTA 2019:104

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# 1. Abstract


**Background**

Osteoporosis is an asymptomatic change of bone mineral density (BMD) that implies an increased risk for bone fractures. Currently, osteoporosis is an underdiagnosed and undertreated condition. Bone mineral density (BMD) measurement using dual-energy x-ray absorptiometry (DXA). DXA is not recommended for general screening due to high costs and low sensitivity. A Fracture Risk Assessment Tool (FRAX) that estimates the 10-year fracture risk is freely available online, and The Swedish National Board of Health and Welfare recommends thresholds of a FRAX-determined fracture risk of >15% for medical and radiological examination, and a FRAX-determined fracture risk of >30% for medication with bone-active drugs which can decrease the fracture risk by 40%.

Dental radiographs have been suggested as a method for identifying individuals with high fracture risk. Dental radiographs could be used for prediction of fracture risk as they are commonly taken as part of dental care in a large proportion of the population. Devices and expertise to interpret dental radiographs are already established in dental clinics.

**Objectives**

1. To assess whether analysis of trabecular bone pattern in an intraoral radiograph and/or panoramic radiograph can predict fracture risk in adults without diagnosed osteoporosis, compared with fracture risk prediction with DXA or with FRAX.
2. To test sensitivity and specificity for identification of osteoporosis, as compared with DXA.

**Methods**

A systematic literature search was conducted in April 2018 in Medline, Embase, the Cochrane Library, and several HTA-databases. The included studies were critically appraised using the QUADAS-2 tool for quality assessment of diagnostic accuracy studies and the certainties of evidence were assessed using the GRADE approach.

**Main results**

Two cohort studies and one cross-sectional study were included in the analysis.

The two cohort studies evaluated the use of trabecular bone pattern in dental radiographs of the lower jaw for prediction of bone fractures in women with a follow-up of 10 to 15 years. The relative risk of fracture was significantly higher for women with sparse trabecular bone pattern, identified by visual assessment of dental radiographs by dentists, in one of the studies (including two cohorts), and by digital software assessment in the other study. Visual assessment in the second study did not show significant results. Taken together, the two studies showed that trabecular bone evaluation on dental radiographs may predict fractures in adults without prior diagnosed osteoporosis. Low certainty of evidence (GRADE ⊕⊕○○).

The cross-sectional study on digital analyses of trabecular bone pattern, in relation to osteoporosis (defined as DXA BMD T-score ≤ -2.5), reported a sensitivity of 0.70 (95% CI 0.62 to 0.78), and a specificity of 0.69 (95% CI 0.64 to 0.73). Based on this study, it is uncertain whether digital image analysis of trabecular bone correlates to DXA BMD T-score ≤ -2.5. Very low certainty of evidence (GRADE ⊕○○○).

**Concluding remarks**

Based on low certainty of evidence (GRADE ⊕⊕○○) trabecular bone evaluation on dental radiographs may provide a technique to predict fracture in adults without prior diagnosed osteoporosis. It is uncertain whether digital image analysis of trabecular bone correlates to DXA BMD T-score ≤ -2.5. Very low certainty of evidence (GRADE ⊕○○○). The potential benefits of fracture risk assessments based on dental radiographs must be weighed against an increase in time consumed for assessment of dental radiographs, a growing number of referrals to DXA, as well as false positive and negative test results. In addition, information on the prevalence, test sensitivity and specificity for fracture prediction is pivotal regarding the economic consequences of the technology.

# 2. Svensk sammanfattning – Swedish summary


**Bakgrund**

Osteoporos (benskörhet) är en asymtomatisk förändring av skelettets mineralinnehåll, eller bentäthet (eng. *bone mineral density*, BMD), som innebär en ökad risk för frakturer. Idag är osteoporos ett underdiagnostiserat och underbehandlat tillstånd. Mätning av bentäthet med *Dual-energy X-ray Absorptiometry* (DXA) rekommenderas inte som screening på grund av höga kostnader och låg sensitivitet. I stället används ett frakturbedömnings-instrument, "*Fracture Risk Assessment Tool*" (FRAX), som uppskattar den 10-åriga frakturrisken och som är tillgängligt kostnadsfritt på Internet. Socialstyrelsen rekommenderar ett tröskelvärde på FRAX på > 15 % för att göra en medicinsk undersökning och på > 30 % för att sätta in behandling med benaktiva läkemedel. Frakturförebyggande behandlingar kan minska frakturrisken med upp till 40 % hos patienter som har diagnostiserats med osteoporos.

Tandröntgen har föreslagits som en metod för att identifiera individer med hög frakturrisk. Tandröntgen skulle kunna användas för att prediktera frakturrisk eftersom det är en del av sedvanlig tandvård för en stor andel av befolkningen. Både röntgenutrustning och kompetens för bedömning av röntgenbilderna finns på tandvårdsmottagningar.

**Syfte**

Att utvärdera huruvida analys av trabekulärt benmönster i underkäken i intraorala röntgenbilder/panoramaröntgenbilder kan användas för bedömning av frakturrisk hos vuxna utan osteoporosdiagnos, jämfört med riskbedömning med DXA eller FRAX, samt att utvärdera tandröntgenanalysernas sensitivitet och specificitet avseende osteoporos, jämfört med DXA.

**Metod**

Systematiska litteratursökningar utfördes i april 2018 i Medline, Embase, Cochrane Library, och flera HTA-databaser. De inkluderade studierna granskades med QUADAS-2-instrumentet för kvalitetsgranskning av diagnostiska studier och tillförlitligheten till det vetenskapliga underlaget värderades enligt GRADE.

**Resultat**

Två kohortstudier och en tvärsnittsstudie inkluderades i analysen.

Båda kohortstudierna utvärderade analys av trabekulärt benmönster i underkäken i tandröntgenbilder för frakturprediktion hos kvinnor (10–15 års uppföljning). Den relativa frakturrisken var signifikant högre hos kvinnor med glest trabekulärt benmönster, som identifierats genom visuell analys av röntgenbilderna av tandläkare (i den ena studien med två kohorter), och med hjälp av datorprogram i den andra studien. I den andra studien nådde inte den visuella analysen av benmönstret signifikanta resultat avseende frakturrisk. Tillsammans visar de två kohortstudierna att analys av trabekulärt benmönster i tandröntgenbilder möjligen kan användas för frakturprediktion hos vuxna utan tidigare osteoporosdiagnos. Begränsat vetenskapligt underlag (GRADE ⊕⊕○○).

Tvärsnittsstudien med digital analys av trabekulärt benmönster i tandröntgenbilder, i förhållande till osteoporos (definierad som DXA bentäthet T-värde ≤ -2.5), uppvisade en sensitivitet på 0.70 (95 % konfidensintervall 0.62 till 0.78), och specificitet på 0.69 (95 % konfidensintervall 0.64 till 0.73). Baserat på denna studie är det osäkert huruvida digital analys av trabekulärt benmönster i tandröntgenbilder korrelerar med DXA bentäthet T-värde ≤ -2.5. Otillräckligt vetenskapligt underlag (GRADE ⊕○○○).

**Sammanfattande slutsats**

Begränsat vetenskapligt underlag (GRADE ⊕⊕○○) indikerar att analys av trabekulärt benmönster i tandröntgenbilder kan vara en teknik för frakturprediktion hos vuxna utan tidigare diagnosticerad osteoporos. Otillräckligt vetenskapligt underlag (GRADE ⊕○○○) indikerar att det är osäkert huruvida digital analys av trabekulärt benmönster i tandröntgenbilder korrelerar med DXA bentäthet T-värde ≤ -2.5. Det bör beaktas att analys av tandröntgen för prediktion av frakturrisk skulle innebära en viss tidsåtgång för bedömning av röntgenbilder för tandläkare, ett ökande antal remisser till DXA, samt falskt positiva och negativa resultat som måste tas i beräkning och balanseras mot den potentiella nyttan. Prevalens, samt sensitivitet och specificitet avseende frakturprediktion är avgörande avseende de ekonomiska konsekvenserna av teknologin.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 19 December 2018

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# 3. Summary of Findings

| Outcomes | Study design<br>Number of studies | Relative risk (95%CI) | | Certainty of evidence GRADE* |
|---|---|---|---|---|
| | | Index test | Reference test | |
| **Fracture prediction** | 1 cohort study with 15-year follow-up (n=136) | Visual evaluation of sparse trabeculation<br>RR 1.52<br>95% CI: 0.56 to 4.11<br><br>Software evaluation of bone texture<br>RR 4.74<br>95% CI: 1.49 to 15.04 | FRAX ≥7% (without BMD)<br>RR 1.34<br>95% CI: 0.56-3.20 | ⊕⊕○○[1] |
| | 1 cohort study with 10-year follow-up, two overlapping groups (n=499 and 412, respectively) | Visual evaluation of sparse trabeculation<br>RR 2.09<br>95% CI: 1.3 to 3.5<br>RR 3.7<br>95% CI: 2.2-6.4 | FRAX ≥15% (without BMD)<br>RR 1.85<br>95% CI: 0.7 to 5.6<br>RR 4.1<br>95% CI: 2.4-7.2 | |
| **Sensitivity and specificity for DXA BMD T-score ≤ -2.5** | 1 cross-sectional study (n=671) | Sensitivity: 0.70<br>95% CI: 0.62 to 0.78 | Specificity: 0.69<br>95% CI: 0.64 to 0.73 | ⊕○○○[2] |

BMD = bone mineral density, CI = confidence interval, DXA = Dual-energy X-ray absorptiometry, FRAX = fracture risk assessment tool, Jaw-X: a computer software, based on an image processing algorithm, OR = Odds ratio, RR = relative risk.

Footnotes:

[1] Some study limitations (patient flow not clearly described), uncertain precision (few events), and large effect (up-grade one step).

[2] Serious study limitations (missing data, blinding not reported, x-ray location of analysis on preference), and serious imprecision (hypothesis generating design, low prevalence).

*** Certainty of evidence**

| | |
|---|---|
| High certainty ⊕⊕⊕⊕ | We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate certainty ⊕⊕⊕○ | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| Low certainty ⊕⊕○○ | Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. |
| Very low certainty ⊕○○○ | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. |

# 4. Abbreviations/Acronyms

| | |
|---|---|
| AUC | Area under curve |
| AR | Absolute risk |
| BMD | Bone mineral density |
| DXA | Dual-energy X-ray absorptiometry |
| FRAX | Fracture risk assessment tool |
| HTA | Health technology assessment |
| OR | Odds ratio |
| RCT | Randomized controlled trial |
| RR | Relative risk |
| ROC | Receiver operating characteristic |
| VGR | Region Västra Götaland |
| WHO | World Health Organization |

# 5. Background

**Disease/disorder of interest and its degree of severity**

People with osteoporosis are at increased risk of fractures upon mechanical forces that would not ordinarily result in fracture (i.e. fragility fractures or low-trauma fractures), which may occur upon low energy injuries such as a fall (Kanis *et al*., 2001). Osteoporosis is asymptomatic and causes no pain. Thus, the condition may not become evident until fractures occur. Some fracture risk factors cannot be altered, such as age and heredity, whereas e.g. life-style and nutrition can be modified.

Osteoporotic fractures that occur in the hip or the vertebrae are associated with high morbidity and mortality. Approximately 20% of those who suffer from a hip fracture die within the following year (Socialstyrelsen, 2012), not because of the fracture itself but due to comorbidity and/or thrombosis as a result of inactivity. Only 30% of patients regain their former physical capacity after a hip fracture. Both hip and vertebral fractures lead to decreased health-related quality of life and an increased risk of reduced physical function or immobility. Hip fracture is associated with a 20% and vertebral fractures with up to a 35% decrease in health-related quality of life (Borgström *et al*., 2006). Vertebral fractures cause back pain and loss of height.

Although professional organizations have made recommendations for fracture prevention in different populations, there is no consensus on a gold standard for screening method. However, the osteoporosis diagnosis is commonly determined by measuring bone mineral density (BMD) with dual-energy x-ray absorptiometry (DXA) (Tu *et al*., 2018).

BMD measured with DXA is not recommended for screening of the population because of its high costs and low sensitivity. The sensitivity for prediction of fractures varies depending on the age of the individuals from 20-70%, with the highest sensitivity for individuals over the age of 80 years (Sanders *et al*., 2006).

The risk of fracture is highest among women with osteoporosis, but 50-70% of all fragility fractures occur in individuals with osteopenia (Pasco *et al*., 2006; Sanders *et al*., 2006). It is only in the very old (>80 years) that most fractures occur in women with osteoporosis. Of the women sustaining fractures, 80% of 50 to 59-year olds did not have osteoporosis, 50% of 60 to 79-year olds did not have osteoporosis, and even among those over 80 years of age, 30% did not have osteoporosis based on DXA measurements. Therefore, reducing the population burden of fractures requires attention not only to osteoporotic women but also to women with osteopenia (Sanders *et al*., 2006).

Using the term osteoporotic fractures for fragility fractures is misleading because it implies that the fractures occur in a group of women identifiable by measurement of BMD.

The Fracture Risk Assessment Tool (FRAX) estimates the 10-year fracture risk and is freely accessible on the Internet (FRAX® Fracture Risk Assessment Tool, 2008). FRAX was developed in 2008, by Centre for metabolic bone diseases, University of Sheffield, UK. FRAX is based on clinical variables such as age, weight, previous fracture, heredity, current smoking, and use of oral glucocorticoids, rheumatoid arthritis, and alcohol intake (≥3 units daily). A value for BMD can be included in FRAX, but the tool can also be used without BMD. If a response is missing, the tool calculates the probability of future fracture as if the response was "no". Inclusion of BMD increases the predictive value of FRAX. The Swedish National Board of Health and Welfare recommends a FRAX (without DXA) determined fracture risk of >15% as a threshold for medical examination and referral for BMD with DXA, and a FRAX-determined risk of >30% as threshold for medication with bone-active drugs (Socialstyrelsen, 2012).

The sensitivity and specificity levels of FRAX vary widely depending on, for example, defined population thresholds, as described in Kanis *et al*. (2007). In four studies included in a systematic review by National Clinical Guideline Centre UK (2012), FRAX (without BMD) at 10% threshold, had sensitivity ranging from 50 to 100 % (95% CI: 46% to 100%) and specificity from 0 to 72 % (95% CI: 0% to 73%), whereas at the 20% threshold the sensitivity and specificity were from 16 to 29% (95% CI: 13%–31 %), and from 81 to 93% (95% CI: 80% to 94%), respectively. At the FRAX 30 % threshold the sensitivity ranged from 4 to 10% (95% CI: 3% to 11%), and the specificity from 96 to 99% (95% CI: 95%–99%) (Bolland *et al*., 2011; Ensrud *et al*., 2009; Fraser *et al*., 2011; Leslie *et al*., 2010).

### Prevalence and incidence

In 2012, the number of individuals in Region Västra Götaland who suffered an osteoporotic fracture was 5,061, and the number of individuals with a hip fracture was 1,845 (Västra Götalandsregionen, 2013). In 2017, the number of individuals in Region Västra Götaland who suffered an osteoporotic fracture was 4,784 (Västra Götalandsregionen, Vårddatabas Vega, 2019).

### Present assessment

For individuals with a FRAX score of >15% (without DXA), BMD with central DXA of the hip and the lumbar vertebrae should be measured.

### The normal pathway through the healthcare system and current wait time for medical assessment/treatment

The normal pathway through the healthcare system in Region Västra Götaland follows a 'fracture liaison service' (*frakturkedja*) in which individuals older than 50 years with an osteoporotic fracture are identified by a hospital 'fracture chain coordinator' and receive a treatment plan from the Osteoporosis Unit.
After the fracture, the patient may be referred to a general practitioner. They evaluate FRAX and refer for DXA (at the osteoporosis ward) if FRAX is >15%. Patients can also self-refer for DXA assessment.
Present waiting time for DXA in Region Västra Götaland is 4-6 months (Sahlgrenska Universitetssjukhuset, 2018). If treatment is recommended after DXA measurements, it is possible to join a 'School of osteoporosis' at Sahlgrenska University Hospital, Mölndal. The general practitioner prescribes the medication and meets the patient annually. The effect of the medication is evaluated by a new DXA at least every second year. The osteoporotic ward reports the DXA results as well as their recommended time point for the next DXA assessment to the general practitioner. Treatment duration, e.g. with alendronic acid, is 4-6 years. Thereafter the medication can be paused for 1-2 years upon which a new FRAX and possibly DXA can take place.

### Number of patients per year who undergo current treatment regimen

Bone-active treatments are available and decrease the fracture risk by 40% (Socialstyrelsen, 2014). Still, only 12% of patients with fragility fractures were treated with bone-specific medication between 2005 and 2012.

With the recent introduction of fracture liason services, this proportion is likely to have increased in the subsequent years. Approximately 14% were treated with vitamin D and calcium (18% of hip fracture patients) according to the National Board of Health and Welfare in Sweden. Thus, osteoporosis is currently considered underdiagnosed and the associated risk for fracture undertreated.

**Present recommendations from medical societies or health authorities**

According to the National Board of Health and Welfare (Socialstyrelsen, 2014), prevention measures and/or treatment should be applied to:

- women aged at least 59 years with previous fragility/low-trauma fracture
- men aged at least 70 years with previous fragility/low-trauma fracture
- individuals with FRAX >15% (without BMD measurements)

According to regional guidelines in Region Västra Götaland (Västra Götalandsregionen, 2018), individuals older than 50 years with a fragility fracture should be identified by a hospital fracture chain coordinator and receive a treatment plan from the Osteoporosis Unit. For high risk patients, for example old people who are hospitalized due to the first hip fracture or vertebral compression, medical treatment should be initiated already before hospital discharge.

In primary care, the general practitioners should use FRAX to identify risk patients and then DXA to measure BMD, and thereafter when indicated, provide treatment with bisphosphonate (e.g. alendronic acid or zoledronic acid) or denosumab.

**Health Technology at issue: Trabecular bone pattern assessment in dental radiographs as fracture risk indicator**

BMD measured with DXA and FRAX are the two methods currently used for identifying individuals with an increased risk for fractures. It is a problem that even those at high risk, who e.g. already have sustained a fracture, are not necessarily assessed. Currently, efforts are made to establish new diagnostic and treatment pathways, involving various healthcare providers.

Dental radiographs have been suggested as a method for identifying individuals with high fracture risk (Sundh *et al*., 2017; Jonasson *et al.,* 2011). There are digital as well as visual techniques for assessing fracture risk using dental radiographs. The digital techniques assess the thickness and degree of connection of the trabeculae (Lee and White, 2005; White *et al*., 2005a), the transition from trabeculae to inter-trabecular spaces, or the number and size of the marrow spaces between the trabeculae (Jonasson and Billhult, 2013).

The visual method uses three reference images (A-C) to categorize the trabecular bone. A) sparse trabeculation (few trabeculae, large marrow spaces and an impression of more radiolucency in the image); B) heterogeneous trabeculation (both dense and sparse trabeculation where dense bone is found more adjacent to the tooth crowns and the sparse bone is more apically situated, or difficulties sorting the trabecular pattern under dense or sparse); C) dense homogeneous trabeculation (many trabeculae are connected to each other and small but many marrow spaces in the entire radiographed area).

In this HTA-report, two different types of dental radiographic images were used for bone pattern analyses: the intraoral radiograph and panoramic radiograph. The intraoral radiograph is the standard technique used by dentists and dental hygienists during regular dental check-ups. An intraoral radiograph covers a relatively limited area of the jaw bone, typically the area surrounding two to three teeth. In contrast a panoramic radiograph is obtained by scanning a larger area covering the upper and lower jaws and surrounding tissues, basically from ear to ear, and gives an overview of a large area. However, the intraoral radiograph has a higher resolution compared with the panoramic radiograph and is therefore more detailed.

The advantages of using dental radiographs as a screening tool for the assessment of fracture risk may be:

- A large proportion of the adult population visit their dentist annually
- Individual intraoral radiographs taken on a regular basis in dental examinations use largely similar projections and exposures, making them suitable for comparisons over time.
- All dental care clinics already have intraoral X-ray devices. Panoramic radiographic equipment is however not found at a majority of general dental clinics.
- Dentists are well trained in interpreting dental radiographs and prevention is one of the dentists' primary tasks.
- Periapical radiograph is the type of image that permits evaluation of the trabecular bone well besides diagnosis of jaw infections usually from the root canal/pulp system of teeth, while bitewing radiographs images tooth crowns and cervical part of the trabecular bone, close to the tooth crown. Therefore, these radiographs are mostly used for diagnosis of caries and periodontitis. A panoramic radiograph reveals both jaws, including the mandibular cortex and all present teeth as well as other anatomic structures within the oral and maxillofacial area.
- Periapical radiographs are used regularly during dental examinations, albeit on diagnostic indications.
- The remodelling rate of the trabecular bone is much higher than that of the cortical bone (Kanis, 1994). Furthermore, the remodelling rate of the mandibular alveolar bone is generally higher than that of the trabecular bone in other parts of the skeleton (Huja *et al*. 2006), which facilitates fracture risk detection using dental radiographs.

# Objective

**The main question for the current HTA project**
Can analysis of trabecular bone pattern in an intraoral radiograph and/or panoramic radiograph predict fracture risk in adults without diagnosed osteoporosis, compared with DXA or FRAX?

**PICO:** (*P=Patient I=Intervention C=Comparison O=Outcome*)

| | |
|---|---|
| **P** | Adults without diagnosed osteoporosis |
| **I** | 1: Analysis of trabecular pattern in an intraoral radiograph<br>2: Analysis of trabecular pattern in a panoramic radiograph |
| **C** | 1: Dual-energy X-ray absorptiometry (DXA) value<br>2: Fracture risk assessment tool (FRAX) score |
| **O** | <u>Critical for decision making</u><br>Fracture prediction<br><br><u>Important for decision making</u><br>Test sensitivity and specificity for osteoporosis defined as with DXA T-score ≤ -2.5<br><br><u>Less important for decision making</u><br>Risks and/or complications (not related to radiation) |

For a detailed description, see Appendix 1.

# 6. Methods

### Systematic literature search (Appendix 1)

During April 2018 two authors (IS, AL) performed systematic searches in Medline, Embase, the Cochrane Library and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional studies. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment.

### Critical appraisal and certainty of evidence

The included studies, their design, and patient characteristics are presented in Appendix 2. Excluded studies, with reasons for exclusion, are presented in Appendix 3. The included studies have been critically appraised using the QUADAS-2 tool for quality assessment of diagnostic accuracy studies (Whiting *et al*., 2011; QUADAS-2, n.d.). The findings of each study have been summarized per outcome in Appendix 4. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7). Certainty of evidence was assessed according to the GRADE approach (Atkins *et al*., 2004; GRADE Working group).

### Ongoing research

A search in www.clinicaltrials.gov (2018-09-05) was conducted with the keywords:
*(Dental Radiography OR Intraoral OR Intra-oral OR Periapical OR Peri-apical OR Periapex OR Peri-apex OR PanORamic OR Pantomography OR Pantomographies OR Orthopantomography OR Orthopantomographies OR Panoramic Radiography OR Panoramic Radiographies OR Radiovisiograph OR Scanora OR Scanoras OR Visualix OR Visualices OR Digora OR Digoras OR Sens-A-Ray OR Sens A Ray OR SensARay)*
*AND*
*(Cancellous or Spongy or Trabecular OR Intertrabecular or Bone Density OR Bone Densities OR Bone Mineral Density OR Bone Mineral Densities OR BMD or Bone mineral content OR Bone Mineral Contents OR Bone texture).*

# 7. Results

### Systematic literature search (Appendix 1)

The literature search identified 2,377 articles after removal of duplicates. After reading the abstracts 2,301 articles were excluded. Another 34 articles were excluded by two authors after reading the articles in full text. The remaining 42 articles were sent to all participants of the project group, and three articles (two cohort studies and one cross-sectional) were finally included in the assessment (Appendix 2).

### Results

Three publications, reporting on two cohort studies and one cross-sectional study, met the inclusion criteria for the central question (Jonasson and Billhult, 2013; Sundh *et al*., 2017; Verheij *et al*., 2009).
The two cohort studies had fracture as outcome (Jonasson and Billhult, 2013; Sundh *et al*., 2017). Both studies had low precision mainly due to small to moderate sample sizes and few fracture events.
The cross-sectional study (Verheij *et al*., 2009) calculated sensitivity and specificity for using a digital image analysis of trabecular bone pattern in the mandible as an indicator of BMD, which was assessed by DXA scan of lumbar spine and hip.

This study employed a hypothesis-generating design, in which several different markers were used to identify the potentially best sensitivity and specificity of osteoporosis diagnosis, thereby introducing a risk for significant results by chance. Furthermore, the regions of interest in the dental radiographs were selected manually and blinding of the assessments was not reported.

**Analysis of trabecular bone pattern in intraoral or panoramic radiographs to predict fracture risk in adults compared with DXA**

*Outcomes, critical for decision-making*

**Fracture (Appendix 4.1)**
Two cohort studies that compared evaluation of trabecular bone pattern in intraoral or panoramic radiographs with DXA and/or FRAX reported fracture as an outcome. Both studies had limitations regarding precision (see above). The settings differed between the studies. In the cohort study by Jonasson and Billhult (2013) the information regarding the studied population was unclear with regard to sample selection and exclusion criteria.

The cohort study by Jonasson and Billhult (2013), with up to 15-year follow-up, reported relative fracture risks assessed with different methods (correlated to subsequent fracture rates).
The computer-based assessment of trabecular bone in intraoral radiographs resulted in a RR of fracture of 4.74 (95% CI: 1.49 to 15.04, $p<0.05$), and FRAX combined with BMD (DXA forearm) in a RR of fracture of 2.53 (95% CI: 1.13 to 5.63, $p<0.05$). The other fracture risk assessments were not statistically significant (e.g. visual evaluation, software tool Jaw-X, and FRAX without BMD). The absolute fracture rate was 19.1% in the total study population.

The cohort study by Sundh *et al*. (2017), studied two population samples of randomly selected women over a mean period of 10 years (a substantial number of women participated in both cohorts). The fracture rates during the follow-up periods were compared between the groups that were considered at risk (FRAX > 15% and/or sparse trabeculation), with those without identified fracture risk factors.
With visual assessments of panoramic radiographs for detection of sparse trabeculation, for fracture prediction, in the first cohort (years 1980-1992, age 50-66 years, 499 women), the RR for fractures was 2.09 (95% CI: 1.3 to 3.5). In the second cohort (1992-2002, age 62-78 years, 412 women), the RR for fractures was 3.7 (95% CI: 2.2 to 6.4). For fracture prediction with FRAX alone (threshold >15%) the corresponding RRs were 1.85 (95% CI: 0.7 to 5.6) in the 1980-1992 cohort, and 4.1 (95% CI: 2.4 to 7.2) in the 1992-2002 cohort, respectively.
The absolute fracture rates were 14.2% in the 1980-1992 cohort and 16.3% in the 1992-2002 cohort.

Conclusion
Trabecular bone evaluation on dental radiographs may be used to predict fracture in adults without a prior diagnosis of osteoporosis. Low certainty of evidence (GRADE ⊕⊕◯◯)

*Outcomes, important for decision-making*

**Test sensitivity and specificity for osteoporosis measured with DXA (Appendix 4.2)**
One cross sectional study (Verheij *et al*., 2009) reported sensitivity and specificity of trabecular bone pattern assessment in intraoral- and panoramic radiographs (as index test) for prediction of osteoporosis, defined as DXA obtained BMD T-score ≤ - 2.5.
The study employed a hypothesis-generating design and had several study limitations (see above), and the mean age of the study population was 54.8 years (SD 6.1).

Regarding morphological, digital analyses of trabecular bone pattern, in relation to DXA BMD T-score ≤ -2.5, the sensitivity for osteoporosis, defined as BMD T-score ≤ -2.5, was 0.70 (95% CI: 0.62 to 0.78), and the corresponding specificity was 0.69 (95% CI: 0.64 to 0.73).

Conclusion

It is uncertain whether digital image analysis of trabecular bone correlates to DXA BMD T-score ≤ -2.5. Very low certainty of evidence (GRADE ⊕◯◯◯).

*Outcomes, less important for decision making*

**Risks and/or complications (not related to radiation)**

No studies reported complications.

# 8. Ethical aspects

For patients diagnosed with osteoporosis, currently available treatments have the potential to improve health-related quality of life and longevity. However, implementing the proposed new test method, with analyses of intraoral radiographs, will lead to increased referrals from dental care to primary care, more healthcare visits and laboratory tests. This could affect the availability of primary care for other medical conditions. For dental health care providers, implementing the new method would add another diagnostic task to the ordinary dental examination which may lead to inappropriate prioritisations.

Due to the potential harmful effects of ionizing radiation, every radiographic examination must be justified (one extra intraoral radiograph with effective dose of <1.5uSv (Ludlow, 2008), is comparable to 1 day of natural background radiation). If one assumes that assessment of trabeculation is performed on already existing radiographs, the proposed method will not add any extra exposure, and it would be valuable to be able to utilize the information obtained from dental radiographs for an additional purpose, such as prediction of fracture risk.

What are the risks, from an individual perspective, given a false positive assessment of osteoporosis? This question is highly dependent on how these individuals will be taken care of in the public health care system. Would it add further, unnecessary, laboratory tests and/or examinations? Regarding radiation risk, the exposure to radiation from a BMD examination using DXA leads to an effective radiation dose in the range of 2.4-13.3µSv (i.e. 0.0024-0.013 mSv), depending on equipment, region and tissue weighting factors used (Blake *et al*., 2006). This radiation dose is minuscule in relation to the annual mean radiation dose in Sweden of 2.4 mSv (for non-smokers) (Andersson, 2007). The radiation dose from one intraoral dental radiograph is about 0.01 mSv (Andersson, 2007).
In Sweden DXA examinations are conducted based on medical history and clinical examination and thus, only individuals at risk for disease are examined. Another issue to be considered is how information given by a dentist could affect the psychological well-being of an individual, who came for an ordinary dental examination, but got unexpected information about a hypothetical diagnosis of osteoporosis and then must wait several months for a final assessment regarding this diagnosis.

The benefit of the new prediction method for fractures (or osteoporosis) in dental care may be clear given the high number of older individuals/patients attending dental care on a regular basis. The method does not discriminate between gender, ethnicity or age, thus not violating ethical principles in health care, but individuals that do not attend to dental check-ups on a regular basis would be missed.

However, prediction of fractures in dental practices would imply that resources in dental care and health care are used for the new technique instead for other conditions needing attention. This possible scenario must be weighed against the advantage of fracture prediction - reducing the number of skeletal fractures in the older population and reducing the cost for treatment and suffering for individuals, but also in a societal perspective.

# 9. Organisational aspects

### Time frame for the putative introduction of the new health technology

Currently we are mainly working with secondary fragility fracture prevention, since osteoporosis is most commonly suspected only after an individual already has sustained a fracture. With the new technology we would aim for primary prevention – i.e. to identify patients before their first fracture. Introducing a new fracture prediction method may take a long time.

### Present use of the technology in other hospitals in Region Västra Götaland

Evaluation of trabecular bone pattern on dental radiographs for the purpose of assessing osteoporosis-related fracture risk is presently not used in clinical practice in Region Västra Götaland, nor elsewhere to our knowledge.

The guidelines from the National Board of Health and Welfare today recommend that when osteoporosis is suspected, the healthcare services should assess the fracture risk by FRAX and, if necessary, conduct a DXA (Socialstyrelsen, 2014).

### Consequences of the new health technology for personnel

A majority (about 80-85%) of older adults make regular visits to their dental care clinics. Today dental intraoral (periapical) radiographs are already used as a complement to the examination of the teeth and the alveolar bone.

A closer communication and collaboration between the dental care clinics and the medical professions, in the first line Primary Health Care Centres, will be necessary if the new technology is introduced and when osteoporosis can be suspected from evaluation of the radiographs. If individuals with sparse bone structure on dental radiographs are referred for evaluation to Primary Health Care Centres, there will be an increase in the number of visits, DXA screenings, and blood tests to exclude secondary osteoporosis. The need for DXA should first be assessed based on medical history, symptoms and FRAX-score. Early identification of individuals with osteoporosis would enable doctors to treat causes of secondary osteoporosis or initiate bone-strengthening medication timely, thereby preventing a number of osteoporosis-related fractures. A screening visit, including clinical examination and reviewing the medical history and possible symptoms of the individual, may limit the need for DXA screenings.

### Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

A more widespread use of dental radiographs for prediction of fractures is likely to increase the demand for resources in the Primary Health Care Centres in the short term. Also, a possible organisational challenge is the need of communicating information for several patients between dental- and primary care. However, in the long term, introduction of the new technology intends to increase the detection and treatment of osteoporosis. This would be expected to include health improvements in patients suffering from osteoporosis as well as a better health-related quality of life, together with a greater functional ability and a reduced number of fractures (Socialstyrelsen, 2014). For health care, the preventive work by dental and primary care would aim to reduce the number of fractures that need to be treated in orthopaedic surgery and rehabilitation.

# 10. Economic aspects

### Present costs of currently used technologies

The current technologies used for identifying patients at risk for osteoporotic fracture are FRAX and BMD measurement using DXA, with costs of about 1,500 SEK per physician visit including a FRAX, and an additional 1,000 SEK per DXA (which requires the associated visit, thus a total cost of 2,500 SEK for DXA measurement).

The intervention (dental intraoral radiographs) is intended to substantially increase the number of analysed individuals, which implies that for the large mass of individuals analysed, there is no current alternative technology used and thus no associated costs. Initially, the intervention will therefore be cost-increasing compared to the current technology. At a second stage, analyses of dental radiographs for fracture prediction, earlier diagnosis and treatment could potentially reduce the costs associated with hip and other fractures.

### Model of the economic consequences of the new technology

Figure 1 shows a simple model of the economic consequences of introducing dental intraoral radiographs with the associated resource use (costs) in each path of the model. In our analysis we assume a situation in which trabecular bone pattern assessment in dental radiographs would be implemented for the population aged 60 and above in Region Västra Götaland.

The first event is the additional time spent for analysis of the dental intraoral radiograph, which is estimated to consume approx. 5 minutes of dentist time per screening, and if a patient at risk is identified an additional 10 minutes of dentist time to write a referral. The dentist time cost is based on the average wage of dentists including social fees and mandatory (for the employer) retirement savings, i.e. the full market price per dentist hour. For an individual with a referral, additional costs will result due to a primary care visit, lab tests, and potentially also a DXA. If treatment is initiated, the drug treatment regimen includes Alendronate or Zoledronic acid and Calcium with Vitamin D.

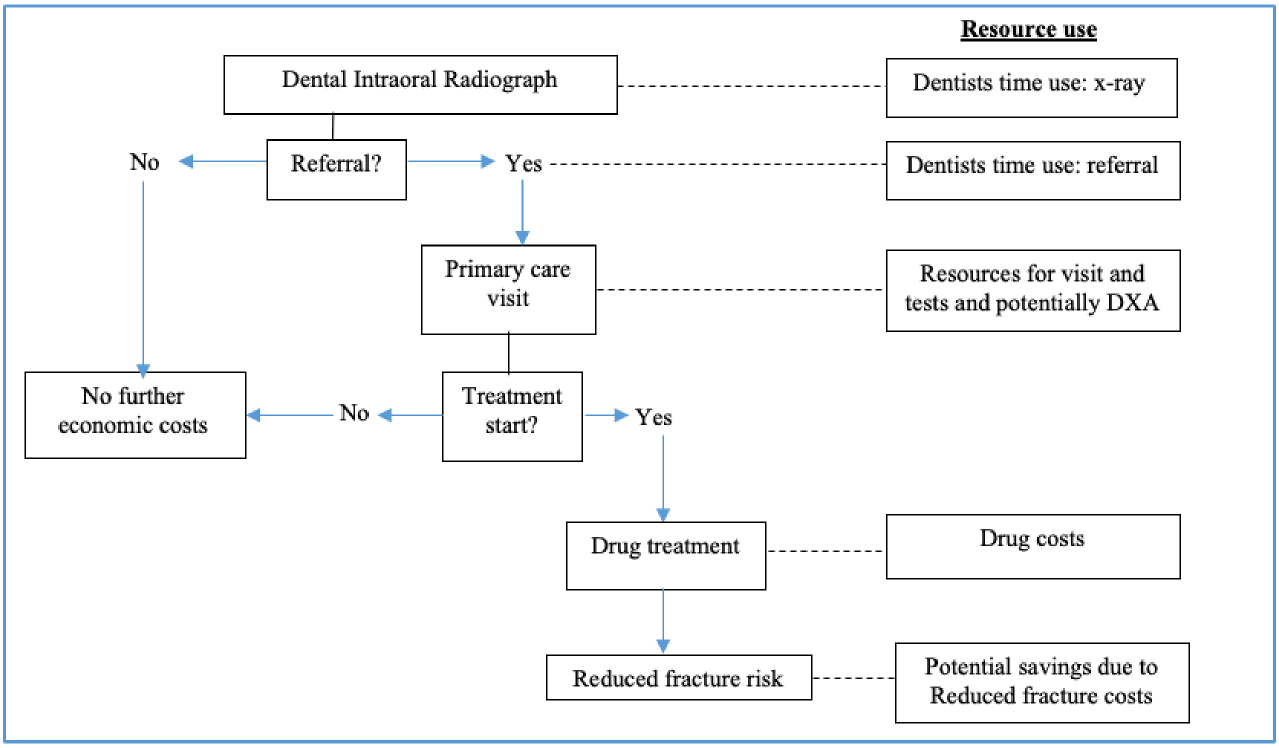
Finally, an important aspect from an economic perspective is the potential savings that may materialise if currently untreated individuals with osteoporosis are identified and provided preventive treatment. Fractures, especially hip fractures, come with a substantial health care cost, and bone-active treatments have been shown to reduce the risk of hip and other fractures.

The challenge with an economic analysis of introducing dental intraoral radiographs is that for many of the relevant epidemiological and clinical variables there are great uncertainties regarding the magnitude of the effects, for example:

- What is the prevalence of currently unidentified osteoporosis patients that could potentially be diagnosed and treated based on introducing dental intraoral radiographs?
- What is the sensitivity and specificity of the dental intraoral radiographs for identification of osteoporosis?
- What is the risk reduction in terms of fewer incident fractures for patients who would receive drug treatment?

Considering the uncertainties, we present the economic consequences both as intervals including 95% of the most likely outcomes as well as the result in different scenarios.

**Figure 1.** Overview of cost consequences




*Assumptions for the economic analysis*
As described, there are many uncertainties related to the economic consequences of introducing dental intraoral radiographs, and Table 1 lists the variables that is part of the economic analysis and also the assumptions used to produce the results in this report.

Some variables are assumed to be relatively certain and have a modest impact on the result (e.g.  dentist screening time of 5 minutes), whereas there are substantial uncertainties in other cases (e.g. prevalence of undiagnosed osteoporosis patients, the sensitivity and specificity of the dental intraoral radiographs, fracture risk reduction if initiating drug treatment, etc.). The variables with large uncertainty and with substantial impact on the results were analysed using a range of reasonable values, and the uncertainty of these analyses are shown using 95% credible intervals.

**Cost per reduced fracture**
Table 2 shows the cost per each reduced fracture if introducing dental intraoral radiographs and how it varies with different scenarios/assumptions. The mean estimate is based on the values listed in Table 1, and for variables with uncertainties it is based on the mid-point of the uncertainty range in Table 1.

The different scenarios show how the cost varies when the value of a parameter is changed. The mean estimate shows that the cost per reduced fracture is 28,300 SEK, which implies that for each reduced fracture the health care costs increase by 28,300 SEK. The reduced costs due to fewer fractures are thus not enough to compensate for the increased costs due to analysing, diagnosing and screening additional individuals.

**Table 1. Assumptions for the economic analysis**

| Variable | Value for primary analysis |
|---|---|
| Dentists' time use costs per hour (incl. social fees) | 410 SEK |
| Dental Intraoral Radiograph screening time | 5 min |
| Referral time for identified individuals | 10 min |
| Prevalence of undiagnosed osteoporosis | 3% to 17% |
| Sensitivity for identification of osteoporosis | 60% - 80% |
| Specificity for identification of osteoporosis | 60% - 80% |
| Cost per physician visit | 1,500 SEK |
| Cost of lab tests | 500 SEK |
| Proportion of DXA for individuals with referral | 50% to 100% |
| Cost per DXA | 1,000 SEK |
| Proportion of identified patients (with DXA) receiving/complying treatment | 60% to 100% |
| Alendronic acid | 198 SEK/year |
| Zoledronic acid | 2608 SEK/year |
| Calcium with Vitamin D | 588 SEK/year |
| Years of drug treatment | 5 years |
| Fracture risk reduction of drug treatment | 30% - 40% |
| Savings per prevented fracture (adjusted for prevalence of different fractures) | 55,000 SEK |

**Table 2.** Cost per reduced fracture

| Scenario | Cost per reduced fracture |
|---|---|
| **Mean estimate** | **28 300 SEK** |
| Prevalence of undiagnosed osteoporosis patients is (instead of 10%): | |
| …3% | 141 900 SEK |
| …17% | 8 200 SEK |
| Proportion of diagnosed patients receiving and complying with treatment is (instead of 80%): | |
| …60% | 46 600 SEK |
| …100% | 17 600 SEK |
| Fracture risk reduction of drug treatment is (instead of 35%): | |
| …30% | 42 200 SEK |
| …40% | 17 800 SEK |
| Sensitivity and specificity for identification of osteoporosis is (instead of 70%): | |
| …60% | 52 000 SEK |
| …80% | 10 400 SEK |

The results in Table 2 for the different scenarios show that the cost per reduced fracture varies from 8,200 SEK to 141,900 SEK. The variable with the largest impact is the prevalence of undiagnosed osteoporosis. A relatively higher prevalence implies a much lower cost per reduced fracture, i.e. an economically more beneficial outcome. This is a representation of the fact that dental radiographs as a screening method is more economically motivated in populations with a higher level of undiagnosed osteoporosis. Regarding the sensitivity and specificity, the latter is the most important from an economic perspective. The reason is that false positive results (poor specificity) will create an increased volume of patients to primary care for evaluation where there is no benefit.

### Cost per screened person (budget impact)

Table 3 shows the cost per screened person, which can be seen as the budget impact of introducing dental radiographs in the population aged 60 and above. The results are shown from a dental care perspective, which only considers dental care cost consequences, and a health care perspective that only considers health care cost consequences. Table 3 also shows the joint health care and dental cost consequences with and without taking future fracture risk reductions into consideration.

The results show the interval of the expected mean cost per each person screened based on the assumptions (with uncertainties) listed in Table 1.

**Table 3.** Budget impact per screened person with dental intraoral radiograph

| Perspective | Cost per screened person (95% credible interval) |
|---|---|
| Dental care | 57 SEK |
| Health care | 1 060 SEK to 2 190 SEK |
| Dental and health care with fracture risk reduction | 130 SEK to 970 SEK |

From a dental care perspective, the new technology will imply a cost at around 57 SEK per person screened. Hence, if introducing dental intraoral radiographs each dental visit including a screening will be expected to cost 57 SEK more.

The largest cost impact is seen at the health care perspective where each person screened will increase costs by 1,060 to 2,190 SEK per screened person. This is mainly driven by the inflow of additional physician visits, tests and (for some) prescription drug expenses. The large interval of the expected cost increase is caused by the great uncertainties in mainly the underlying epidemiological and clinical data on the chain of consequences with dental intraoral radiographs.

Finally, the joint dental and healthcare perspective accounting for future reductions in fracture risk shows that the cost per screened person will be in the range of 130 to 970 SEK.

### Possibility to adopt and use the new technology within the present budget

The results indicate that it will not be possible to fit the new technology within the present budget. Especially the increase in primary care visits due to identifying more at-risk patients and the increase in prescription drugs use will require additional budget funds, or it will displace some of the currently provided primary care.

### Available economic evaluations or cost advantages/disadvantages

No economic evaluations or cost-consequence or budget-impact analysis studies of the new technology were identified in the published literature.

## 11. Discussion

The present HTA report identified a lack of longitudinal investigations with fracture as an outcome. Only two studies fulfilled the inclusion criteria. In addition, diagnostic studies with osteoporosis as outcome were virtually absent, and only one study fulfilled the inclusion criteria. All three studies included solely females. Based on low certainty of evidence (GRADE ⊕⊕◯◯), trabecular bone evaluation on dental radiographs may predict fracture in adults without prior diagnosed osteoporosis. It is uncertain whether digital image analysis of trabecular bone correlates to DXA BMD T-score ≤ -2.5 (very low certainty of evidence, GRADE ⊕◯◯◯).

Very few fracture events were reported by Jonasson and Billhult (2013). Several participants increased their bone density (BMD measured by DXA) during the study period, by improving nutrition and physical activity after information was given. Osteoporotic participants were referred to their respective primary care centre or general practitioner for further examination and were prescribed medication calcium and vitamin D supplements and sometimes oestrogen too.

At the time of the study's baseline (1996), no national guidelines were available for the treatment of osteoporosis nor any established diagnostic criteria.

FRAX and visual trabecular pattern could be easily assessed in the dental clinic. Although beyond the scope of this report, it seems that combining assessments of mandibular bone trabeculation with other risk factors could increase the fracture predictive value substantially, especially in older individuals (Sundh *et al*., 2017).

Having no risk factor was associated with a very low risk for fracture (1.5%), whereas the relative risk of fractures increased by 16 to 23 times when combining various risk factors (Sundh *et al*., 2017). By comparing the gradient of risks reported by Sundh *et al*. (2017) and that reported by Kanis *et al*. (2007), it seems that the combination of a FRAX score of > 15% and the finding of mandibular sparse trabeculation in dental radiographs could predict major osteoporotic fractures to approximately the same extent as FRAX combined with BMD measurements using DXA (Kanis *et al*., 2007; Sundh *et al*., 2017).

Sensitivity and specificity for sparse trabeculation as fracture predictor were 27% and 88%, respectively (Jonasson and Billhult, 2013). These rates are comparable to the sensitivity and specificity for osteoporosis found in a study by Lindh *et al*. (2008) (sensitivity 28.2% and specificity 90.8%) where the trabecular pattern was evaluated as indicator of osteoporosis.

In the younger cohort (Sundh *et al*., 2017), sparse trabeculation as fracture predictor had a sensitivity of 61% and specificity 66%. For FRAX, sensitivity was 25% and specificity 94% (without DXA). In the older cohort, sparse trabeculation as fracture predictor had a sensitivity of 78% and specificity 57%, whereas for FRAX, sensitivity was 79% and specificity 58% (Sundh *et al*., 2017).

There is no gold standard established for fracture prediction (except the subsequent outcome itself). However, BMD measured by DXA of the hip and FRAX are currently the most widely investigated methods and were therefore chosen as reference standards (comparisons) in this report.

In order to obtain the best directness regarding the clinical setting of general dentistry, the population of interest for this report was defined as "adults without diagnosed osteoporosis". The technology at issue was "analysis of trabecular pattern in dental radiographs". Again, for best directness, as well as clinical relevance, evaluations of cortical bone were omitted because general dental practices may not have panoramic radiographic equipment. Panoramic radiographs also have lower resolution than intraoral radiographs and more practice is needed to perform trabecular assessment with panoramic radiographs than with periapical radiographs. Thus, for this purpose only periapical radiographs are suitable.

Currently used methods of analysing the trabecular bone of the mandible may not be better for detecting the risk of developing osteoporosis and risk for fragility fractures than the standard methods used in common examination pathways in general health care, such as FRAX and DXA. Thus, a knowledge gap is present as of today, however new emerging analysis tools based on digital algorithms will be developed which may further improve predictive values.

Consequence of assessment of trabecular bone pattern in dental radiographs for fracture risk are that more time would be required for this assessment, the number of referrals to primary care for medical examinations and eventually for DXA would increase, and a number of false positive and negative test results would be expected - all of which should be taken into account and balanced against the potential benefits. The prevalence, test sensitivity and specificity for fracture prediction is pivotal regarding the economic consequences of the technology.

# 12. Future perspectives

### Scientific knowledge gaps

Larger prospective studies in varying settings with fracture as outcome are warranted. One study from the Prospective Population Study of Women in Gothenburg, Sweden (Jonasson *et al*., 2011, 2013) with the same data set as Sundh *et al*. (2017) also demonstrates the potential benefit of using dental radiographs as fracture predictors. Long-term studies assessing trabecular pattern in intraoral and panoramic radiographs are also needed, as well as comparisons with up-to-date FRAX and DXA measures. Furthermore, existing research lacks data on men as well as on populations with a wide range of older ages. Because people today tend to live longer, we need a better understanding of the potential role of trabecular pattern assessment.

Despite advances and ongoing intense efforts to evaluate and develop optimal software algorithms for artificial intelligence, gaps remain in this area before it can be applied in dental care. Several research groups are developing varying texture analysis methods for measuring trabecular volume, spacing, and connectivity by computed tomography, magnetic resonance, and cone beam computed tomography (Geraets, Lindh and Verheij, 2012; Geraets *et al*., 2007; Kavitha, 2015, 2016;
Kathirvelue and Anburajan, 2014; Koh *et al*., 2012; Licks *et al*., 2010; Lee and White, 2005, Lurie *et al*., 2012; White *et al*., 2005a; Brasileiro *et al*., 2017; Mostafa *et al*., 2016), but presently the cost and complexity of these methods limit their utility for clinical routine and as a screening method.

### Ongoing research

A search in www.clinicaltrials.gov (2018-09-05) yielded 48 records.
None of the trials were relevant for the question at issue.

# 13. Participants in the project

### The question was nominated by

Magnus Hakeberg, DDS, Professor, Department of Behavioural and Community Dentistry, Institute of Odontology, The Sahlgrenska Academy, University of Gothenburg and Clinic of Oral medicine, Public Dental Service, Region Västra Götaland, Gothenburg, Sweden.

### Participating healthcare professionals

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**Declaration of interests**

Grethe Jonasson, Dominique Hange and Magnus Hakeberg are co-authors of the publication Sundh *et al*., 2017. Grethe Jonasson also is co-author of the publication Jonasson and Billhult, 2013.

**Project time**

The HTA was accomplished during the period of April to December 2018.
Literature searches were made in April 2018.

**Appendix 1: Search strategy, study selection and references**

**Question(s) at issue:**
Can analysis of trabecular bone pattern in an intraoral radiograph and/or panoramic radiograph predict fracture risk in adults without diagnosed osteoporosis, compared with DXA or FRAX?

**PICO:** (*P=Patient I=Intervention C=Comparison O=Outcome*)

| | |
|---|---|
| **P1** | Adults without diagnosed osteoporosis |
| **I** | 1: Analysis of trabecular pattern in an intraoral radiograph<br>2: Analysis of trabecular pattern in a panoramic radiograph |
| **C** | 1: Dual-energy X-ray absorptiometry (DXA) value<br>2: Fracture risk assessment tool (FRAX) score |
| **O** | <u>Critical for decision making</u><br>Fracture prediction<br><br><u>Important for decision making</u><br>Test sensitivity and specificity for osteoporosis defined as with DXA T-score ≤ -2.5<br><br><u>Less important for decision making</u><br>Risks and/or complications (not related to radiation) |

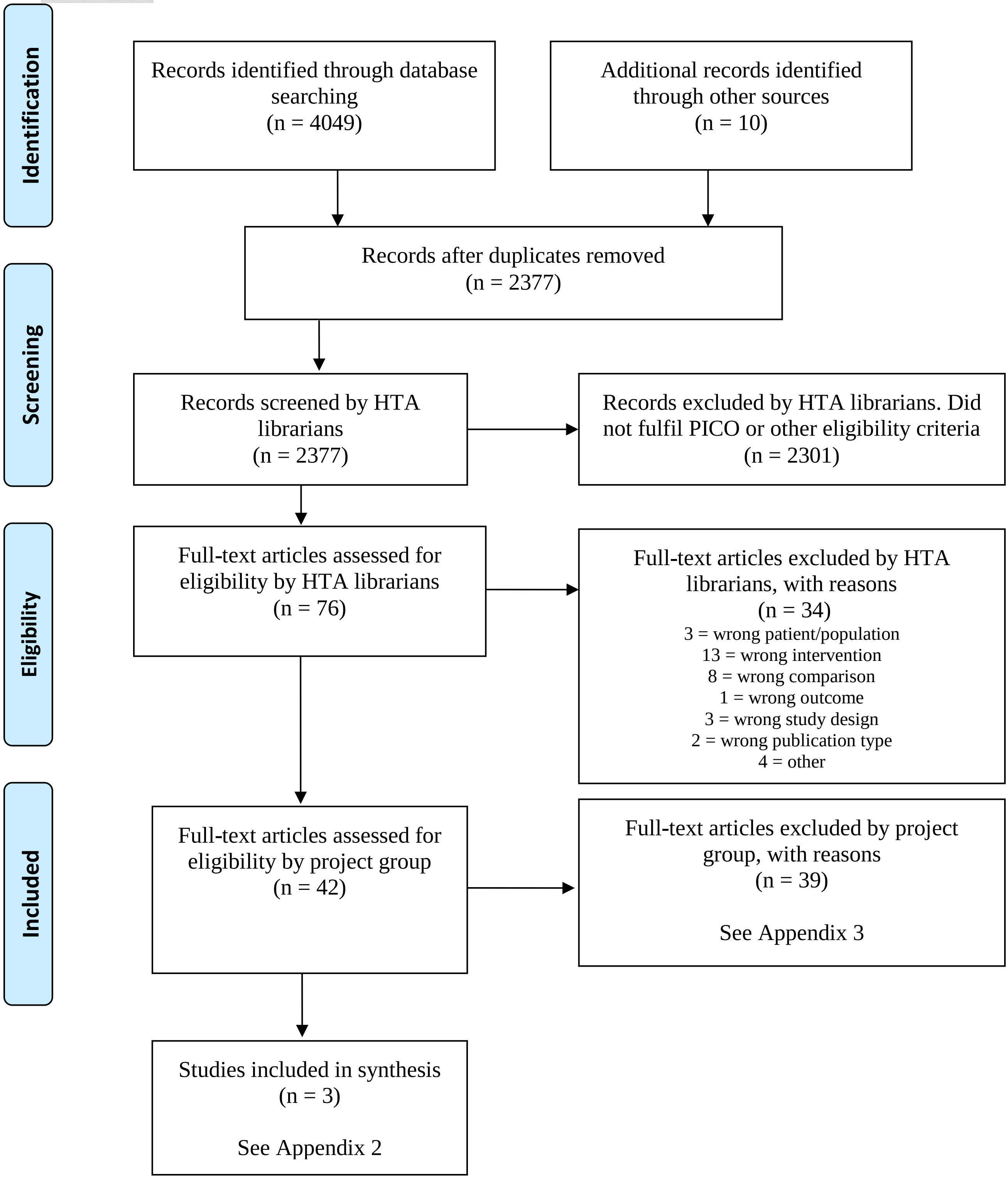
<u>**Eligibility criteria**</u>

**Study design:**
Systematic reviews
Randomised controlled trials
Cohort studies
Case series ≥ 500 patients

**Language:**
English, Swedish, Danish, Norwegian, Finnish

**Publication date:** 1990-

## Selection process – flow diagram



**Database:** Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
**Date:** 2018-04-13
**No. of results:** 1822 ref.

| # | Searches | Results |
|---|---|---|
| 1 | exp Radiography, Dental/ | 20222 |
| 2 | ((Dental or Intraoral or Intra-oral or periapical or peri-apical or Periapex or Peri-apex or tooth or teeth or mandib* or maxilla* or jaw*) and (radiograph* or radiolog* or x-ray* or xray* or imag*)).ab,ti. | 51183 |
| 3 | (Panoramic* or Pantomogra* or Orthopantomogra* or radiovisiograph* or Scanora* or Visualix or Visualices or Digora* or Sens-A-Ray* or Sens A Ray* or SensARay*).ab,ti. | 8385 |
| 4 | 1 or 2 or 3 | 64416 |
| 5 | exp Cancellous Bone/ | 423 |
| 6 | exp Bone Density/ | 48104 |
| 7 | (Cancellous or spongy or trabecul* or Intertrabecul* or Bone densit* or Bone mineral densit* or BMD or Bone mineral content* or bone textur*).ab,ti. | 91404 |
| 8 | 5 or 6 or 7 | 103817 |
| 9 | 4 and 8 | 2488 |
| 10 | (animals not (animals and humans)).sh. | 4413620 |
| 11 | 9 not 10 | 1998 |
| 12 | (comment or editorial or letter).pt. | 1621349 |
| 13 | 11 not 12 | 1992 |
| 14 | limit 13 to yr="1990 -Current" | 1927 |
| **15** | **limit 14 to (danish or english or finnish or norwegian or swedish)** | **1822** |

**Database:** Embase 1974 to 2018 April 12
**Date:** 2018-04-13
**No. of results:** 1960 ref.

| # | Searches | Results |
|---|---|---|
| 1 | exp dental radiology/ | 17537 |
| 2 | exp panoramic radiography/ | 9114 |
| 3 | ((Dental or Intraoral or Intra-oral or periapical or peri-apical or Periapex or Peri-apex or tooth or teeth or mandib* or maxilla* or jaw*) and (radiograph* or radiolog* or x-ray* or xray* or imag*)).ab,ti. | 54349 |
| 4 | (Panoramic* or Pantomogra* or Orthopantomogra* or radiovisiograph* or Scanora* or Visualix or Visualices or Digora* or Sens-A-Ray* or Sens A Ray* or SensARay*).ab,ti. | 8715 |
| 5 | 1 or 2 or 3 or 4 | 71261 |
| 6 | exp trabecular bone/ | 17957 |
| 7 | exp bone density/ | 80632 |
| 8 | (Cancellous or spongy or trabecul* or Intertrabecul* or Bone densit* or Bone mineral densit* or BMD or Bone mineral content* or Bone texture*).ab,ti. | 126297 |
| 9 | 6 or 7 or 8 | 148006 |
| 10 | 5 and 9 | 2798 |
| 11 | (animal not (animal and human)).sh. | 1402293 |
| 12 | 10 not 11 | 2545 |
| 13 | limit 12 to yr="1990 -Current" | 2444 |
| 14 | limit 13 to (danish or english or finnish or norwegian or swedish) | 2269 |
| **15** | **limit 14 to (article or conference paper or "review")** | **1960** |

———————————————————————————————————————————

**Database:** The Cochrane Library
**Date:** 2018-04-13
**No. of results:** 267
*Cochrane Reviews* (1)
*Trials* (266)

| # | Searches | Results |
|---|---|---|
| #1 | MeSH descriptor: [Radiography, Dental] explode all trees | 458 |
| #2 | ((Dental or Intraoral or Intra-oral or periapical or peri-apical or Periapex or Peri-apex or tooth or teeth or mandib* or maxilla* or jaw*) and (radiograph* or radiolog* or x-ray* or xray* or imag*)):ti,ab,kw (Word variations have been searched) | 3697 |
| #3 | Panoramic* or Pantomogra* or Orthopantomogra* or radiovisiograph* or Scanora* or Visualix or Visualices or Digora* or Sens-A-Ray* or Sens A Ray* or SensARay*:ti,ab,kw (Word variations have been searched) | 296 |
| #4 | #1 or #2 or #3 | 3782 |
| #5 | MeSH descriptor: [Cancellous Bone] explode all trees | 8 |
| #6 | MeSH descriptor: [Bone Density] explode all trees | 4591 |
| #7 | Cancellous or spongy or trabecul* or Intertrabecul* or "Bone densit*" or "Bone mineral densit*" or BMD or "Bone mineral content*" or "Bone texture*":ti,ab,kw (Word variations have been searched) | 11008 |
| #8 | #5 or #6 or #7 | 11008 |
| **#9** | **#4 and #8 Publication Year from 1990 to 2018** | **267** |

The websites of **SBU** and **Folkehelseinstituttet** were visited 2018-04-13.
Nothing relevant to the question at issue was found.

**Reference lists**
A comprehensive review of reference lists brought 10 new records.

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Västra Götalandsregionen, Vårddatabas Vega, 2019.

**Appendix 2 –** Characteristics of included studies
**Project:** Trabecular bone pattern assessment in dental radiographs for screening of fracture risk

| **Author Year Country** | **Study design** | **Study duration (years)** | **Study groups; Index vs reference** | **Patients (n)** | **Mean age (years)** | **Men (%)** | **Outcome variables** |
|---|---|---|---|---|---|---|---|
| Jonasson & Billhult 2013, Sweden. | Cohort | 15 years, 1996-2011 | Intraoral radiograph vs. FRAX and/or BMD (by DXA) | 136 | 64.1<br>SD 11.2<br>Range 35-94 | 0 | Fracture risk |
| Sundh et al 2017, Sweden. | Cohort | 10 years 1980-1992<br>10 years 1992-2002 | Panoramic radiograph vs. FRAX | 499 (1980-1992)<br>412 (1992-2002) | Range 50-66 (1980-1992)<br>Range 62-78 (1992-2002) | 0 | Fracture risk |
| Verheij et al 2009, Belgium, Greece, The Netherlands, Sweden, United Kingdom | Cross sectional | Not reported | Panoramic and intraoral radiographs vs. BMD (by DXA) | 607 | 54.8<br>SD 6.1<br>Range 45-71 | 0 | Sensitivity and specificity for osteoporosis measured with DXA* |

BMD: Bone mineral density, DXA:Dual-energy X-ray absorptiometry, FRAX: Fracture risk assessment tool* i.e. DXA BMD T-score -2.5

**Appendix 3.**
**Project:** Trabecular bone pattern assessment in dental radiographs for screening of fracture risk
Excluded articles

| Author, year | Reason for exclusion |
|---|---|
| Ay, S., 2005 | Wrong I |
| Engel, M.B., 1994 | Wrong I |
| Geraets W.G., 2012 | Wrong O |
| Geraets W.G., 2007 | Wrong O |
| Geraets W.G., 2008 | Wrong O |
| Hedström L., 2010 | Wrong C |
| Jonasson G., 2009 | Wrong O |
| Jonasson G., 2015 | Wrong O |
| Jonasson G., 2001 | Wrong O |
| Jonasson G., 2006 | Wrong O |
| Jonasson G., 2007 | Wrong O |
| Jonasson G., 2011 | Duplicate material of Jonasson G., 2013 |
| Jonasson G., 2013 | Case series not reporting risks or complications |
| Kathirvelu D and Anburajan M., 2014 | Wrong O |
| Kavitha M.S., 2015 | Wrong I |
| Kavitha M.S., 2016 | Wrong I |
| Khojastehpour L., 2013 | Wrong I |
| Koh K.J., 2012 | Wrong P |
| Law A.N., 1996 | Wrong P |
| Lee B.D., 2005 | Data not extractable |
| Leite A.F., 2015 | Wrong I |
| Licks R., 2010 | Wrong O |
| Lindh C., 2008 | Wrong P |
| Lopez- Lopez, J., 2015 | Wrong P |
| Lundstrom A., 2001 | Wrong P |
| Lurie A., 2012 | Wrong I |
| Mohajery M., 1992 | Wrong I |
| Mohammad A.R., 1996 | Wrong P |
| Nackaerts, O,. 2008 | Wrong P |
| Roberts M.G., 2013 | Wrong I |
| Scheibel, P.C., 2013 | Wrong I |
| Sindeaux R., 2014 | Wrong P |
| Takishi Y., 2013 | Wrong I |
| Tosoni G.M., 2006 | Wrong P |
| White S.C., 1999 | Wrong P |
| White S.C., 2005a | Case series not reporting risks or complications |
| White S.C., 2005b | Wrong P |
| Yasar F., 2006 | Wrong O |
| Yilmaz H.H., 2004 | Wrong P |

**Appendix 4.1**
**Project:** Trabecular bone pattern assessment in dental radiographs for screening of fracture risk
**Outcome variable:** Fracture prediction

| |
|---|
| * + No or minor problems<br>? Some problems<br>- Major problems |

| Author year country | Study design | Number of patients n= | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Index test<br><br>(Trabecular bone pattern assessment in dental radiographs) | Reference test<br><br>(FRAX, BMD) | | | | |
| Jonasson & Billhult 2013, Sweden | Observational, prospective cohort study | 1996<br>n=166<br><br>2011<br>n=136<br>replied<br>(14 died) | n=30 | *Fracture prediction:*<br><br>Visual evaluation, sparse trabeculation<br>RR 1.52<br>95% CI: 0.56 to 4.11, n.s.<br>AR 35%<br><br>Jaw-X (software)<br>RR 1.87<br>95% CI: 0.73 to 4.71, n.s.<br><br>Bone texture (software)<br>RR 4.74<br>95% CI: 1.49 to 15.04, $p<0.05$ | *Fracture prediction:*<br><br>FRAX with BMD[2]<br>RR 2.53<br>95% CI: 1.13 to 5.63, $p<0.05$<br><br>FRAX without BMD<br>RR 1.34<br>95% CI: 0.56 to 3.20, n.s.<br><br>BMD<br>RR 2.37<br>95% CI: 0.93 to 6.02, n.s. | BMD: DXA forearm<br><br>To calculate the RR, the FRAX value was dichotomised, where ≥ 7% indicated increased risk for fracture.<br><br>Blinded evaluation (according to author Jonasson).<br>Data included in FRAX, from 1996, were analysed retrospectively in 2011 (alcohol consumption was not included in FRAX).<br><br>6 women had T-score ≤ -2.5 | + | ? | - |
| Sundh *et al*., 2017 Sweden | Observational, prospective cohort study | 1980/ 1981<br>n=499<br><br>1992/ 1993<br>n=412 | No dropouts | *Fracture prediction 1980-1992:*<br><br>Visual evaluation, sparse trabeculation<br>RR 2.09<br>95% CI: 1.3 to 3.5<br><br>AR: 23.0%<br><br>OR: 3.03<br>95% CI: 1.81 to 5.08 | *Fracture prediction 1980-1992:*<br><br>FRAX >15%<br>RR 1.85<br>95% CI: 0.7 to 5.6<br><br>AR: 36.7%<br><br>OR: 4.35<br>95% CI: 2.28 to 8.31 | Blinded, according to author.<br>Information on fractures in parents was not available and not included in the FRAX calculation.<br><br>397 participated in both (1980-1993 and 1992-2002) examinations. | + | +/? | - |

**Appendix 4.1**
**Project:** Trabecular bone pattern assessment in dental radiographs for screening of fracture risk
**Outcome variable:** Fracture prediction

| * | + No or minor problems |
|---|---|
| | ? Some problems |
| | - Major problems |

| Author year country | Study design | Number of patients n= | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | **Index test** **(Trabecular bone pattern assessment in dental radiographs)** | **Reference test** **(FRAX, BMD)** | | | | |
| | | | | *Fracture prediction 1992-2002:*<br><br>Visual evaluation, sparse trabeculation<br>RR 3.7<br>95% CI: 2.2 to 6.4<br><br>AR: 26.1%<br><br>OR: 4.57<br>95% CI: 2.47 to 8.45 | *Fracture prediction 1992-2002:*<br><br>FRAX >15%<br>RR 4.1<br>95% CI: 2.4 to 7.2<br><br>AR: 26.9%<br><br>OR: 5.28<br>95% CI: 2.84 to 9.94 | | | | |

AR = Absolute risk, BMD = bone mineral density, Bone texture: a computer software, CI = confidence interval, FRAX = fracture risk assessment tool, Jaw-X: a computer software, based on an image processing algorithm, OR = Odds ratio, RR = relative risk.

**Appendix 4.2**

**Project:** Trabecular bone pattern assessment in dental radiographs for screening of fracture risk

**Outcome variable:** Sensitivity and specificity for osteoporosis measured with DXA*

| * + No or minor problems<br>? Some problems<br>- Major problems |
|---|

| Author year country | Study design | Number of patients n= | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Index test | Reference test | | | | |
| Verheij *et al*., 2009<br>Five countries in Europe:<br>The Netherlands, Belgium, Greece, UK, Sweden. | Observational cross-sectional study | n=671 | n=64 | *Morphological digital analysis of trabecular bone pattern (software)*<br><br>Trabecular pattern<br>For reference test:<br>Sensitivity 0.70<br>(95% CI 0.62 to 0.78)<br>Specificity 0.69<br>(95% CI 0.64 to 0.73) | *DXA hip, spine*<br><br>BMD<br>T-score <= -2.5 | Convenience sample.<br>No pre-determined threshold.<br>Split of Index variable to obtain maximal sensibility and specificity, i.e. no blinding.<br>Mean age 54.8 years (SD 6.1)<br>Regions of interest on the radiographs were chosen by preference.<br>No indication of blinding. | + | ? | - |

BMD = Bone mineral density, CI = Confidence interval, DXA = Dual-energy X-ray absorptiometry.

* i.e. DXA BMD T-score ≤ -2.5

# HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

| | |
|---|---|
| High quality of evidence | = (GRADE⊕⊕⊕⊕ ) |
| Moderate quality of evidence | = (GRADE ⊕⊕⊕O) |
| Low quality of evidence | = (GRADE ⊕⊕OO) |
| Very low quality of evidence | = (GRADE ⊕OOO) |

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

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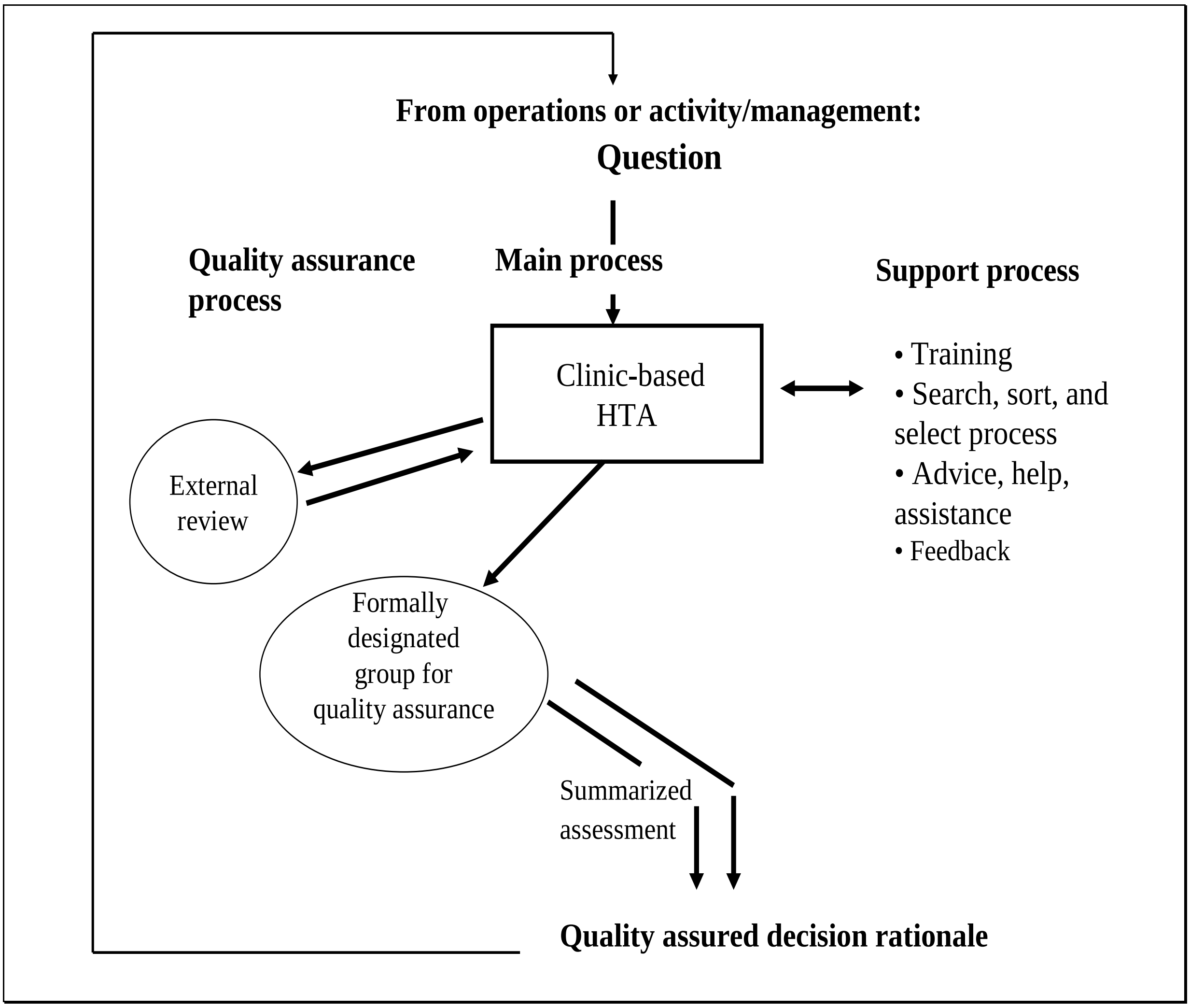
Head of HTA-centrum



From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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