EUnetHTA JA3 WP4 - Other technologies, OTCA19
Comments by external experts on the 2nd draft rapid assessment on Screening for Osteoporosis in the general population

Comments should be submitted not later than 17:00 on Monday 29.07.2019

Please use this form for submitting your comments and please return them to Cecilia de Villiers cecilia.devilliers@hta.lbg.ac.at

Please use the *checklist* for external experts as guidance for your review.

1. Please put each new comment in a new row.
2. Please insert the page number and section number on which your comment applies. If your comment relates to the document as a whole, please put **'general'** in this column.
3. Please provide a description of your comment as specific as possible and preferably also provide a suggestion for rewording. If you wish to draw our attention to published literature, please supply the full reference.
4. Please do not address grammar or language issues as long as they do not affect comprehensibility/readability of the document. The assessment will undergo medical editing prior to its publication.

All comments will be formally responded to in a combined document that will be published on the EUnetHTA website; individual names of the reviewers will be disclosed if reviewers gave their consent.

The 2nd version of the Rapid Assessment on Screening for Osteoporosis in the general population is open to review by external reviewers between 09.07.2019-29.07.2019.

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Mann, Alexander Endokrinologikum Frankfurt, Germany	General		Structure of the report: consistent and comprehensible, however many informations are given repeatedly and there is considerable redundancy. Shortening of the manuscript in this respect should be considered.	1	Thank you very much for this comment. The special structure of the report with its "assessment elements" ("Research questions" at the beginning of each domain) indeed leads to overlaps in content, especially in the TEC and CUR domains. The background to this is to ensure that each assessment element is being addressed. This should make it possible for some interested in a specific subquestion not to have to read the entire report but to provide a concrete answer to a pre-formulated question. If, from your point of view, there are text passages or information that are unnecessary or redundant within an assessment element, we would be very pleased if you could indicate what specifically should be removed. For your information: the template, which was used to write this Rapid REA is currently being revised.
Marta Zwart Salmerón,	3	47	Salmerón	3	Amended, thank you.

Please add extra rows as needed.

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Catalan Health Institute (ICS), Girona, Spain					
Mann, Alexander Endokrinologikum Frankfurt, Germany	Page 9		DVO: replace "german-speaking scientific companies" by german-speaking scientific societies.	2	Amended, thank you.
Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain	12	226	"Identifying patients with fracture risk" would be prefered than "Identifying patients with osteoporosis" as the target is to avoid the fracture not the osteoporosis diagnosis.	2	Thank you. Rephrased in "Identifying patients with osteoporosis-related fracture risk".
Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain	12	235	"Risk factors include gender, age, body mass index (BMI), and lifestyle [1]." There are other major risk factors that should be considered here.	2	Thank you for this comment. The risk factors named here are only exemplary which is expressed by the term "include". We did not intend to provide a complete list of all risk factors at this point as this is the summary section of the assessment in which we tried to be as short and precise as possible. More details are provided in section 3.2.

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Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain	12	256	"Besides general measures to reduce or remove risk factors for osteoporosis and to reduce falls, a range of pharmaceutical compounds have been developed for the treatment of osteoporosis such as bisphosphonates, selective oestrogen receptor modulators etc. [1,8-12]."	2	Amended, thank you.
Johannes Flechtenmacher, Ortho-Zentrum Karlsruhe, Karlsruhe, Germany	12	249	Schould be added: Due to changes in population demography, the annual number of fragility fractures will rise from 3.5 million in 2010 to 4.5 million in 2025, corresponding to an increase of 28%.	2	Thank you for this comment. We found that parts of your proposal are a quotation from https://www.iofbonehealth.org/print/11862, Key statistics from Europe. We added the information that prevalence in osteoporosis rises due to demographic changes in the section "health problem" in line 245.
Johannes Flechtenmacher, Ortho-Zentrum Karlsruhe, Karlsruhe, Germany	15	369	The study from Reid_2018 can be seen very controvercial. For exampel they included patients who were ≥ 65 years old and had a T-Score of -1.0 to -2.5 at either the total hip or the femoral neck on	1	Thank you for this comment. We agree that the study by Reid et al. 2018 differs from the other studies, because study participants had osteopenia (T score −1.0 to −2.5) rather than osteoporosis (T score less than −2.5). For the evaluation of a medical screening test the main

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			either side. After the current guideline of the German-speaking scientific companies on osteology (DVO) most patients with such a DXA T-Score (especially without other risk factors) probably would not be treated with a bisfosfonate.		interest lies in whether the screening and subsequent treatment lead to patient relevant, beneficial effects. If such a benefit is found then it is secondary whether this was achieved via a test that detects the precursor or the disease itself. The DVO guidelines explicitly mention that in the more recent studies fracture rates were reduced by anti-osteoporotic drugs also in postmenopausal women with a T score of -2.0 to -2.5 . Additionally, it is stated that the avoidance of vertebral fractures has also been shown in some studies involving individuals with T scores higher than -2.0. In addition, the European Guideline stated that BMD is one risk factor amongst others for fractures and therefore, the T score threshold of −2.5 might simply be an imperfect criterion, which probably is why the WHO called this an "operational definition" of osteoporosis. Hence, it appears justified also to include the study by Reid et al. 2018. Since the DVO guidelines are limited to the literature available as of June 2016, the study by Reid et al. 2018 is not yet included.

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Mann, Alexander Endokrinologikum Frankfurt, Germany	20	415-418	The Scoop study shows a non significant reduction of total fractures, however Hip fractures are significantly reduced (HR 0,72). The Rose study shows an significant effect concerning Hip fractures in a 2 Step approach – this finding needs to discussed. The Coshiba trial showed an reduction in total number of fractures, but failed statistical significance with p of 0,06. Even if this puts the result into a trend, it appears worth a more intensive discussion.	1	Thank you for this comment. Indeed, we tried to keep the summary section as short and precise as possible. Statistically, no other result regarding symptomatic fractures based on the available data is possible. Please have a look in our discussion section (line 2271 onwards), where we discussed the different hip fracture findings in SCOOP and ROSE and tried to give a plausible rationale for this finding. In addition, you pointed out the per-protocol analysis 2 from ROSE. Indeed, effects of hip fractures were getting statistically significant here. But we also have to keep in mind that this per-protocol analysis 2 only contains a very selected population (women at moderate and high risk of fractures), since only women with a DXA scan are compared to a control population with a FRAX Score ≥ 15%. It is obviously due to this selection that the results are more positive than if the entire screening-treatment approach was examined, as done in the ITT analysis and as required by our research question. In fact, some fracture effect estimators are in favour of the intervention and therefore the resuts cannot be interpreted as

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					proof of no benefit. We have addressed this point more explicitly in a new section of our discussion called "perspective" (see answer on comment below). However, since the effects are not statistically significant, we cannot change the statement of our report.
Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain	20	434	"In conclusion, screening for osteoporosis has probably little or no effect on the incidence of symptomatic fractures. This conclusion is based on overall moderate quality evidence." I do not think it is quite as simple as that. The discussion (p95 2206) brings to a focal point by commenting how the design can influence underestimating the results, especially the contamination bias must be taken into account in the 2 only studies included regarding the fractures outcomes.	1	Thank you for this critical comment. Indeed, we also feel that the results are hard to summarise in a few simple sentences. There are many uncertainties concerning e.g. differences in the screening approach in SCOOP and ROSE, the FRAX calibration in different countries, or the actual treatments received in the strategy design studies. All these thoughts can be found in our discussion section. We do not consider it impossible that studies with e.g. a modified design or with a different screening approach would arrive at different, maybe positive, results. The risk of "underestimating the results", however, cannot be reliably quantified. Since we don't know the direction or strength of biases, it would not be correct to "adjust" the conclusion. In order to highlight the context-dependency and variability of osteoporosis screening (both in clinical studies and real world),

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					we have extended the conclusion (please see our answer on your comment on lines 434-438 below) and added a "perspective section" at the end of our discussion. These additions hopefully address your concerns. "**<u>Perspective</u>** The studies included showed no effect of screening. However, it was notable that the results on hip fractures were inconclusive. It should thus be noted that the results cannot be interpreted as proof of no benefit. Since some potentially dilutive effects may have been present (invitation procedure, risk assessment of the control group), it cannot be ruled out that an improved screening-treatment strategy might deliver other, positive results. When designing future studies, it would be important to ensure that a more stringent (but at the same time implementable) screen-and-treat approach is developed, so that weaknesses in study design resulting in low participation and treatment adherence rates are avoided."
Mann, Alexander Endokrinologikum	20	434-438	I do not agree with the final conclusion, that screening for osteoporosis has probably little or no	1	Thank you for this comment.

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Frankfurt, Germany			effect. As pointed out above effects on hip fractures should be discussed in more detail and possible consequences considered. The manuscript comes to different conclusions as compared to the analysed and cited literature. These differences need to discussed and the respective reasons need to be clarified.		Stating that screening for osteoporosis in postmenopausal women has probably little or no effect does not mean that the current evidence proves the ineffectiveness of screening. We added this argument in a new paragraph called "perspective" (please see answer on comment above). We rephrased the conclusion in so far as we integrated the fact that the results of our Rapid REA are mainly based on a screening strategy containing FRAX and subsequent DXA. Therefore, the results are presumably not applicable to other screening strategies. Additionally, we also referred to the vulnerability of a screening study regarding approach and uptake. Our conclusion now says: "Since the available studies of moderate quality show no effect of screening on the incidence of symptomatic fractures, screening for osteoporosis in postmenopausal women probably has little or no benefit. These findings are mainly based on studies investigating a screening strategy us-ing FRAX for risk assessment and DXA for BMD measurement. The studies included did not allow the evaluation of screening strategies based on other screening tools. As in any screening

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					intervention, benefits and harms are affected by multiple factors such as the type and uptake of screening and treatment. No studies were found on osteoporosis screening in men or younger women." Additionally, we provided a section on "This benefit assessment compared to other systematic reviews and guidelines" (please see 2nd draft line 2344 onwards / 3rd draft line 2355 onwards). Here, we critically discuss our findings with the findings of the current European Guideline on Osteoporosis (Kanis_2019) and the recommendations of the USPSTF (AHRQ report, 2018). From our point of view, it seemed more sensible to compare and discuss our findings with the findings of other systematic reviews than with the findings of included primary studies. We hope that our argumentation is understandable and that the wording of our conclusion now rather reflects your concerns.
Johannes Flechtenmacher, Ortho-Zentrum Karlsruhe,	20	435-438	There are several studys (see for example the FRISBEE Study, Osteoporos Int. 2017 Sep;28(9):2565-2571. doi: 10.1007/s00198-017-4103-3, Bone. 2017 Dec;105:287-291. doi:	1	Thank you for this comment. The studies you cited (Cappelle_2017 [FRISBEE], Weycker_2017, using data from the study of osteoporotic fractures [SOF] and Deloumeau_2017) are single arm

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Karlsruhe, Germany			10.1016/j.bone.2017.08.018.) who show that the occurence of symptomatic fractures depends on the presence of baseline variables (for example fall history). As stated in the study I cannot support your statement		prospective observational studies and therefore do not fulfill the predefined quality of the evidence. Additionally, one of them was investigating women with underlying risk factors so it does not correspond to our target population (i.e. general popuation) either. Observational studies would be appropriate if they were used to further specify the population to be screened in the event of a proven benefit of screening. However, they are not suitable to reverse the negative result of this report. Regarding possibly relevant effect modifiers (i.e. age, anthropometry, BMI, dietary calcium intake, baseline fracture status, recent falls history, BMD, and calculated fracture risk) we found data from only one enrichment design study. Due to its indirectness the quality of the evidence was assessed as low and the results led to the conclusion that the investigated baseline variables may make little or no difference on the occurrence of symptomatic fractures. Therefore, we have to stay with our statement on this topic.
Mann, Alexander Endokrinologikum	24	Col.4	The hazard ratio of 0,72 for hip fractures needs to be discussed (Scoop-Study) Given the clinical	1	Thank you for this comment.

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Frankfurt, Germany			impact of hip fractures, this result may be significant for the overall jugdement.		As stated above, we discussed the hip fracture findings in our discussion section (2nd draft see line 2271 onwards, 3rd draft see line 2281 onwards). We are aware that the results of SCOOP are interpreted in current guidelines and reviews (AHRQ, European Guideline) as an indication of the benefits of screening. However, these works could not yet take into account the results of the ROSE study. We were cautious in interpreting the hip fracture result from SCOOP for several reasons: Firstly, these hip fracture effects were not reflected by a substantial reduction of osteoporotic fractures. Secondly, the effects were not detected in any other study. Neither ROSE (not even in the per-protocol analysis 1, which might be interpreted as to be close to the SCOOP approach [randomisation after risk assessment with FRAX]) nor COSHIBA found a significant reduction in hip fracture. In addition, the pharmacological enrichment design studies did not detect a significant hip fracture reduction either. Thirdly, hip fracture was not the primary outcome of the SCOOP trial and SCOOP authors themselves warned against overemphasizing these results.

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					Of course, we agree with you that hip fractures have a large clinical impact. Unfortunately, for the reasons stated above, data of the available studies did not allow the conclusion that screening reduces the incidence of hip fractures significantly.
Mann, Alexander Endokrinologikum Frankfurt, Germany	24	Col.6	Downgrading was performed due to inconsistency, the inconsistencies should be specified.	1	Thank you for this comment. With the help of a footnote we specified the downgrading due to inconsistency (please see 2nd and 3rd draft SoF table 1-3, footnote "i" and respective description). We interpreted the statistical heterogeneity (I^2 = 87 %) as presumably deriving from differences in study design between SCOOP and ROSE and therefore did not pool the data in a meta-analysis. Please get back to us if you feel that any further information is missing.
Mann, Alexander Endokrinologikum Frankfurt, Germany	28	609-616	As commented above I do not agree with the conclusion.The published studies indicate an effect on hip fractures in elderly women. Given the clinical importance of hip fractures with their effect on mortality and morbidity in old and very old patients these results are not adequately discussed.	1	Thank you for this comment. For author`s reply, please refer to the answer given on your comment on lines 434-438.

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Johannes Flechtenmacher, Ortho-Zentrum Karlsruhe, Karlsruhe, Germany	28	613-614	Zoledronic acid or alendronate is NEVER a part of a screening strategy but allways a therapeutic strategy	1	Thank you for this comment. What should be said here is that the administration of a certain drug has been part of the screening-treatment strategy. We have replaced the term accordingly.
Johannes Flechtenmacher, Ortho-Zentrum Karlsruhe, Karlsruhe, Germany	28	573-574	This statement is not correct. The main finding is that 8 heterogeneous studys (3 RCTs with marker-based strategy design and 5 RCTs with enrichment design) with different study designs, different inculsion criterias and different methods for screening for osteoporosis and some for treatment where identified. The results oft these identified studys show no (or only a small) advantage for the evaluated screening tools with regard to symptomatic fractures.	1	Thank you for this comment. Just like you we are of the opinion that the results presented in this Rapid REA presumably are not applicable to other screening strategies. We stated in our discussion: "Despite the uncertainties described above, the findings of the Rapid REA are in principle considered applicable to the European context but presumably not to alternative screening strategies." We added an additional section in our conclusion addressing this fact. The reason for not evaluating studies investigating a screening strategy including the DVO risk assessment tool simply was that no studies were identified in this respect.

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			These results allow absolutelly no comparison or translation to other screening tools or algorithms. It has to be stated that studys concerning the current guideline of the German-speaking scientific companies on osteology (DVO) have not been evaluated.		For the reworded conclusion please refer to our answer on external expert`s comment on lines 434-438.
Johannes Flechtenmacher, Ortho-Zentrum Karlsruhe, Karlsruhe, Germany	28	610-611	Please see my comments above – this statement is not correct		Please refer to our answer on external expert`s comments on lines 434-438.
Mann, Alexander Endokrinologikum Frankfurt, Germany	38	808	88 Studies were excluded, for the criterion "population". The question arises, if these studies contain relevant findings as to the effect of a screening	1	Thank you very much for this critical comment. We did not identify studies investigating a screening program on a non caucasian population.

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Comments should be submitted not later than 17:00 on Monday 29.07.2019

Comment from *Insert your name, title and affiliation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
			program in other (non caucasian) populations. This should be examined and both a positive or negative result stated		As you can see from our inclusion criteria presented in the tables 2-1 and 2-2 we did not make any restrictions as to ethnicity, age or any other population factors. Only in pharmacological studies it had to be explicitly stated that patients with newly diagnosed osteoporosis were included and / or that patients were identified by screening in the general population. Only then pharmacological studies were deemed to be "enrichment design" studies. Otherwise we excluded studies with "population" as exclusion criterion (i.e. patients with osteoporosis but not being screened from the general population).
Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain	50	1030	The aim is identifying people at risk of fracture for informed decisions alone or in combination with bone mineral density test: lifestyle advice, therapeutic agents...	2	Thank you very much for this feedback. We agree that it is important to state that FRAX can be used with or without BMD measurements. As this has been stated in the next paragraph we have left the text as it is. The aspect of a risk of fracture identified needs to be reversible by treatments which increase bone mass and bone strength has repeatedly been highlighted by the developers of the tool. We therefore think that it is important to have this statement in the

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					text but to make it clear that the aim is obviously to identify patients at risk we have slightly reformulated the statement: "The aim of the FRAX tool is to identify patients with risk factors for a reversible risk of fracture, i.e. a risk of fracture that responds to treatments that change bone mass and strength".
Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain	51	1087	"At the hip" The WHO definitions based on bone mineral density levels are based on DXA measurement at hip or spine.	2	Amended, thank you.
Mann, Alexander Endokrinologikum Frankfurt, Germany	Page 54	line 1198	replace Sevier by Servier, which is the correct company name	3	Amended, thank you.
Mann, Alexander Endokrinologikum Frankfurt, Germany	62	1358-1361	Fracture related deaths are given. On the basis of the given numbers, the results of the Scoop trial should be throughly discussed.	2	Thank you for this comment. We did not have any data on fracture-related deaths in SCOOP or any other study. SCOOP only presented data on overall mortality. The same is true for enrichment design studies

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					reporting deaths (FIT trials, Reid_2018). A comparative discussion was therefore not possible.
Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain	64	1378	"as they share the same risk factors" as they share some risk factors	2	Amended, thank you.
Mann, Alexander Endokrinologikum Frankfurt, Germany	100	2394 - 2401	Even if the summarizing approach is statistically correct, it neglects the dilution effect of non relevant fractures and minimizes a potential benefit of a screening programm on hip fractures in postmenopausal women.	1	Thank you for this comment. In our assessment, all symptomatic fractures are deemed being relevant, namely patient-relevant. If new fractures were described as being only accidently identified on x-ray (which was true for some vertebral fractures not causing any symptoms) we did not consider them patient-relevant. Although we agree that hip fractures are the most severe, we don`t agree with your proposal of putting hip fractures above every other symptomatic fracture and classifying every other symptomatic fracture as "non relevant". In our Rapid REA, we looked at the individual fracture classes separately and found the effects of the hip fractures to be inconclusive: The statistically significant effect of hip fractures

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					can only be seen in SCOOP. Even if in the much larger ROSE study one looks at the per-protocol 1 evaluation (which, comparable to SCOOP, only included subjects with FRAX), this effect does not show up, although here about 50 % more subjects are included than in SCOOP. In order to structure our results, we have reworded and supplemented our conclusion. Please also refer to our answer regarding your comment on lines 434-438 and 609-616.
Marta Zwart Salmerón, Catalan Health Institute (ICS), Girona, Spain, Rafael Azagra Ledesma, Catalan Health Institute (ICS), Barcelona, Spain	100	2395	From our point of view the scarce trials selected in this analysis and the biases are a debatable point to allow us to say that there is evidence that screening for osteoporosis among postmenopausal women has probably little or no benefit with regard to patient-relevant outcomes. Although the systematic review is comprehensive, the few studies included are already a limitation on the conclusions emerging from the document. We would rather specify the most important outcome that is fragility fracture	1	Thank you for this comment. As this argument seems to be closely associated with your comment on line 434, please see our answer above.

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			saying that the data available in this review found that there is no enough evidence that screening for osteoporosis in the general population offer an advantage over no screening with regard to fracture outcome.		
Mann, Alexander Endokrinologikum Frankfurt, Germany	139	Par. 2	The Salt study has been recently published: The effect of a screening and treatment program for the prevention of fractures in older women: a randomized pragmatic trial June 2019 · Journal of Bone and Mineral Research DOI: · 10.1002/jbmr.3815 Thomas Merlijn et al.	1	Thank you for this very valuable hint. Since we performed our last search in May 2019, we could not find the publication of this trial at this stage and unfortunately it is not possible to integrate the findings of this trial in the results of our Rapid REA anymore. To draw the reader's attention to the existence of the results publication we inserted footnotes at the relevant places and we added a passage on this study in our discussion section saying: "The results of the SALT study (n = 11,032 participants) were published after the Rapid REA`s editorial deadline on 13 May 2019 [164]. They could therefore not be considered in this report. However, there was no statistically significant effect on fractures of any type, falls, or mortality. These results should be included in future assessments."

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			The results of this study are important for the manuscript and should be at least recognized and discussed.		Also in this study statistically significant effects on both the primary outcome "fractures" and the secondary outcomes "major osteoporotic fractures", "hip fractures", falls and mortality could not be observed. Future investigations will have to integrate the results of the SALT study in a common analysis but presumably the effects observed in our Rapid REA would not change by adding the effects observed in SALT.
Mann, Alexander Endokrinologikum Frankfurt, Germany			Concluding comment: Considering the available data it appears necessary to specify the criteria for screening: a general approach seems less likely to be effective as compared to a screening program in patients with imminent high risk, i.e. postmenopausal women. It is not the question if but how to screen. This point should be considered and discussed.	1	Thank you very much for this concluding comment. We agree that a well-selected and well-implemented screen-and-treat approach is essential for an optimised benefit-harm ratio of osteoporosis screening. However, we have to rely on the existing evidence, which was already available only from patients with increased risk, namely postmenopausal women. It is not possible to extrapolate the current findings to a hypothetical screening programme which might offer better patient selection, higher participation, and higher adherence rates. Nevertheless, your argument is integrated in the new

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					paragraph called "perspective" but we cannot agree with your positive assumption of osteoporosis screening being effective.

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