Guideline on screening to prevent fragility fractures – reviewer comments and CTFPHC responses

Reviewer 01 (Stakeholder): Dr. Steven Burrell, Canadian Association of Radiologists
Disclosure(s): I am involved with committee work with Osteoporosis Canada including:

- Diagnostic Imaging Knowledge Transfer committee
- Scientific Advisory Council
- Fracture Risk Assessment working group of guidelines committee

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes	Thank you
3. Are the guidelines supported by the evidence?	Yes	Thank you
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Yes	Thank you

5. Do you have any comments or suggestions to improve the guideline?	1. Following an initial screen with clinical FRAX, no guidance is given to support when to move on to BMD other than if therapy is being considered. The recommendations cite a lack of data supporting any **clinical FRAX threshold** for BMD access. Presumably though **many primary care physicians and patients would welcome some guidance in this regard**, although perhaps that is beyond the scope of this project. Since it is assumed FRAX with BMD is more accurate than FRAX without BMD (the premise of the 2-step approach), the intent of the first step is to screen out patients at quite low risk in whom adding BMD is unlikely to alter the decision to initiate therapy. As such, **presumably the threshold to proceed to BMD should be low.**	1. Shared decision-making was recommended based on lower patient acceptability of treatment and knowing that clinical FRAX thresholds for BMD were variable in the trials. Examples of baseline risk and individual risk will be available in an interactive decision aid tool being developed by the Task Force (Fragility Fracture Decision Aid (canadiantaskforce.ca). We have also added this link to the guideline and tried to clarify the rationale behind shared-decision making: "Decision aids may improve understanding of potential benefits and harms of preventive treatment and shared decision-making could better align screening and treatment with patient preferences." "We recommend shared decision-making based on patient acceptability and varying clinical FRAX thresholds for BMD access in the trials."
	2. The approach does not acknowledge the value of the BMD in monitoring changes in patient risk. In making the decision to initiate therapy, the BMD value at a given time point is not the only relevant parameter. **Changes in BMD identify those patients with more rapid bone loss which can influence therapy decisions**. Absence of a baseline BMD precludes incorporating rate of bone loss into future decisions to initiate therapy for osteoporosis.	2. We also did not feel it was prudent to recommend BMD solely for the purpose of baseline BMD unless treatment was being considered. There was no evidence justifying a baseline risk, however we did find information that repeat BMD may be informed by the risk found at the first BMD. See below for screening interval information.
	3. **No guidance is provided on frequency of screening: if there is a decision to not consider therapy at a given time, when should this be re-evaluated?**	3. The task force did not find any evidence on screening intervals in the included trials. However, we do state that, "although some observational studies suggest intervals based on age, baseline BMD

	Presumably this is part of the shared-decision approach.	or absolute fracture risk, repeating BMD at 3-8 years did not improve fracture risk prediction. It is unknown how often to rescreen eligible females; however, rescreening within 8 years does not appear useful.
	4. The recommendation to not screen males >/= 40 is based on a study in males aged ≥ 65 years for which evidence was very uncertain for hip fractures. The broad recommendation to not screen males of any age **does not take into account the increased risk of more elderly males; would there not be an age beyond which male screening would be indicated?** If there are not trials supporting this, **consider adding a statement acknowledging there likely is increased fracture risk and hence screening benefit in more elderly males.** A recommendation against screening of males of any age **runs counter to clinical experience** and initiatives in the clinical osteoporosis community.	4. The evidence for men >65 years was very low certainty and showed no significant reduction in hip fractures. Additionally, there was no evidence for men <65 years. Therefore, considering the potential harms, the task force recommended against screening all men. Since there is relatively low benefit to women as it is, it doesn't make sense to further extrapolate to men even at older ages.
	5. **Spine radiographs** may be used in select circumstances to screen for vertebral fractures, which are generally an indication to initiate therapy due to the high future fracture risk. This is likely beyond the scope of this document.	5. Spinal radiography was included in our analysis if it was part of a screening trial (e.g. BMD + vertebral fracture assessment (VFA)). However, it is outside our scope to recommend when VFA should be performed and this was not consistent across all studies. We have added that "Measurement of bone mineral density involves dual-energy x-ray absorptiometry of the femoral neck (with or without spine or vertebral fracture assessment)."

Reviewer 02 (Stakeholder): Dr. Tripti Papneja, Ontario Rheumatology Association

Disclosure(s): None.

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes Definition of primary care practitioners was very inclusion to include all different health care professionals including physicians, NPs etc.	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes it was succinct and clear and exceptions stated well. Recommendations do not apply to individuals at elevated risk due to previous fragility fracture diagnosis, endocrine or other disorders related to metabolic bone disease, cancer, chronic glucocorticoid use, or those on treatment to prevent fragility fractures.	Thank you
3. Are the guidelines supported by the evidence?	Yes and summarized well in table formats – particularly found Table 2: Accuracy of risk assessment tools (calibrated for Canada) to be very useful. Limitations of the evidence was well documented as well.	Thank you

4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Yes - Key Points Box states - The Task Force recommends not screening females aged 40-64 years and males aged ≥ 40 years (Strong recommendation, very low certainty evidence). Some primary care practitioners (PCPs) only read Key Points Box – therefore it is important to include the exceptions to this recommendation: "Recommendations do not apply to individuals at elevated risk due to previous fragility fracture diagnosis, endocrine or other disorders related to metabolic bone disease, cancer, chronic glucocorticoid use, or those on treatment to prevent fragility fractures."	We have revised the first section from key points to an abstract. We have also revised the excluded population and added this sentence to the abstract: "These recommendations apply to community-dwelling individuals who are not currently on pharmacotherapy to prevent fragility fractures."
5. Do you have any comments or suggestions to improve the guideline?	Introduction states: These may occur in persons with weakened bone structure, often referred to as osteoporosis (2). This is more complex than weakened bone structure (there is quantity and quality of bone that causes fracture and should be clarified) as this article is directed to PCPs not general population only.	We have changed it to: These fractures occur because of weakened bone structure (low bone mass or low mineral density, often referred to as osteoporosis)

Reviewer 03 (Stakeholder): Dr. Michelle Porter, Active Aging Canada

Disclosure(s): N/A

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes	Thank you
3. Are the guidelines supported by the evidence?	Yes	Thank you
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	No	Thank you
5. Do you have any comments or suggestions to improve the guideline?	1. Line 48: "Labelling"of someone as being diagnosed with osteoporosis: What is meant by this word? Stigma? This might need to be explained with a few words rather than just one word. 2. Line 195: "…the task force placed a high value on not expending system-wide resources" 3. Line 230: Are there more details on the participants that were engaged? E.g., ages, education level, etc.	1. Line 48: We have changed it to "labelling, stigma, adverse drug effects" 2. Line 195: We have changed to "the task force placed a high value on not expending system-wide resources" 3. Line 230: Further details are listed in Appendix 6 for the Phase 1 of the patient engagement (e.g., age, sex, education). We have also added more information in Appendix 7 describing the individuals in Phase 2.

Reviewer 04 (Stakeholder): Dr. Rowena Ridout, Osteoporosis Canada

Disclosure(s): I have no relevant financial disclosures
I am currently the Chair of the Scientific Advisory Council for Osteoporosis Canada
I am currently a member of the Pharmacotherapy working group and the steering committee for the Osteoporosis Canada Clinical Practice guideline

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	No 1. The title suggests that the focus is on screening and yet there are comments and assumptions about Rx…. This makes the document unclear (would suggest that screening does not reduce fractures, but rather identifies those who might benefit from further management which can include pharmacotherapy. This is not clear in your document. (starting with lines 11-16 and repeated elsewhere in the text.) 2. There is inconsistent distinction between clinical screening (which would be part of the process of determining higher risk individuals to whom these guidelines do not apply) and DXA screening.	1. The focus of the guideline is indeed on screening and the task force does not make recommendations on treatment. However, we do consider treatment as part of the screening continuum (i.e. screening can identify those who would benefit from treatment). Therefore, information on treatment was used as indirect evidence to inform the screening guideline. We have clarified by adding to the Background that "Screening involves administration of a test or instrument to all individuals in a particular setting to identify who may benefit from further interventions." and to the Scope that "Recommendations on treatment and non-pharmacological prevention are not included." 2. We agree that it is difficult to describe the 2-step screening process. We have tried to clarify by re-naming the process as "risk assessment-first" screening and describing the process in comparison to the "BMD-first" screening that is more common in Canada: "Risk assessment-first" screening includes fracture risk estimation (e.g., FRAX without BMD), followed (if indicated) by BMD. Risk is then re-estimated by adding the BMD T-score to the calculation. "Bone mineral density test-first" screening starts with BMD, usually followed by risk assessment. For both strategies, preventive pharmacotherapy may be offered to those identified as being at high fracture risk. We also clarified in the recommendation: • We recommend risk assessment-first screening to prevent fragility

		fractures in females aged 65 years and older as follows (conditional recommendation, low-certainty evidence): • FRAX: Apply the Canadian clinical FRAX risk assessment tool (without BMD). Use the 10-year absolute risk of MOFs to facilitate shared decision-making about the possible benefits and harms of preventive pharmacotherapy. • BMD + FRAX: After this discussion, if preventive pharmacotherapy is considered, request BMD measurement using DXA of the femoral neck. Then re-estimate fracture risk by adding the BMD T-score into FRAX. We have added throughout the guideline: We recommend risk assessment-first screening for females aged ≥ 65 years…
2. Are the patient groups to whom the guideline is meant to apply clearly described?	The document states only women over age 65 should be screened. It is only in the smaller and somewhat hidden text (and after the text about who to screen) that it is identified that these recommendations are really just for healthy individuals. This may mislead the reader.	After discussion with the Task Force we have decided that the scope of this guideline should include all individuals regardless of risk. This decision was reached due to the difficulty in defining and operationalizing "high risk", and also the fact that these high risk factors (e.g., prior fracture, secondary osteoporosis, parental hip fracture, glucocorticoids) are all part of the FRAX calculation. Therefore, "high risk" can be determined using the FRAX tool as part of the “risk assessment-first” screening process. We also looked at the populations of the 3 main screening trials (SCOOP, ROSE, SALT) and the majority included these high risk populations as a proportion of their screening population. Additionally, those at elevated risk can still benefit from having a shared-decision making conversation with their primary care physician in the context of their calculated elevated risk. Therefore, the guideline can be applied to all individuals other than those already being treated with pharmacotherapy to prevent fragility fractures. We have changed the abstract, recommendations and scope sections to state: The target population for this guideline is community-dwelling adults

		aged 40 years and older, who are not currently on pharmacotherapy to prevent fragility fractures.
3. Are the guidelines supported by the evidence?	1. Not sure about the rationale for avoiding clinical screening in other age groups addressed in this document. The use of a strong recommendation combined with low certainty evidence is justified by placing high importance on non-serious adverse events. Other guidelines have said that there is insufficient evidence but have supported screening older men, and the decision not to do this appears to be based at least in part on data that in 2009 (prior to the 2010 guidelines recommending screening all men >65) only 20% were screened.	1. The strong recommendation not to screen women <65 or men ≥40 years (based on low certainty evidence) was justified by the risk of harms. Beyond just adverse events of treatment, harms also include overdiagnosis which would occur with or without pharmacotherapy. Additionally, the strong recommendation was due to the high value that the task force placed on not expending system-wide resources. In summary, there was no evidence establishing a benefit but there was evidence of harm. Part of the decision was also based on the low screening rates seen in men. Some older data from 2009 needed to be used as this was the only survey which measured "ever screeners" as opposed to the number of screens per year. However, we have clarified by using more recent data in the references for the line: "More recent age standardized data in males aged 40 years and older reveal 8.7% were screened in 2018/19 (69) and 15% of Ontario males 68-70 years (who had never been screened before) were screened in 2017/18 (70) References: 69) Canadian Chronic Disease Surveillance System (CCDSS, 2023) showing an age standardized prevalence rate of 8.7% for males >40 years screened in 2018/19. 70) Ontario data (Jaglal, et al, 2020) showing that 15% of men 68-70 years (who had never been screened before)[1] were screened in 2017/18. If you assume that the Ontario data (most recent and age 65+) is closer to the actual rate, it states that only 15% of eligible males were screened.

[1] Calculation= Rate (per 100) of 'eligible' seniors (aged 68 to 70) who had a BMD test ('eligible' = seniors 68 to 70 who had not had a BMD test in the five years leading up to their 65th birthday).

	2. Statements re bisphosphonates ("may") and dmab ("probably") to not appear to be consistent with the data from the literature (and the distinction may be unclear to the PCP reader). 3. Including all cancer patients as a high risk, which is not supported by the literature – only a small group of cancer patients are actually at risk.	Therefore it appears that following the 2010 guidelines to screen all men >65 years there still was limited uptake. 2. We used the terms "probably reduces" and "may reduce" due to the moderate and low certainty in the evidence respectively. The actual numbers are presented in Appendix 2 which we have now referenced in that section. 3. Agree that not all cancer patients are at risk. We have changed the abstract, recommendations and scope sections to state (see below as well): The target population for this guideline is community-dwelling adults aged 40 years and older, who are not currently on pharmacotherapy to prevent fragility fractures.
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Yes - The statement about individuals to whom the guidelines do not apply omits one of the major risk factors – parental history of hip fracture.	After discussion with the Task Force we have decided that the scope of this guideline should include all individuals regardless of risk. This decision was reached due to the difficulty in defining and operationalizing "high risk", and also the fact that these high risk factors (e.g., prior fracture, secondary osteoporosis, parental hip fracture, glucocorticoids) are all part of the FRAX calculation. Therefore, "high risk" can be determined using the FRAX tool as part of the "risk assessment-first" screening process. We also looked at the populations of the 3 main screening trials (SCOOP, ROSE, SALT) and the majority included these high risk populations as a proportion of their screening population. Additionally, those at elevated risk can still benefit from having a shared-decision making conversation with their primary care physician in the context of their calculated elevated risk. Therefore, the guideline can be applied to all individuals other than those already being treated with pharmacotherapy to prevent fragility fractures. We have changed the abstract, recommendations and scope sections to state:

		The target population for this guideline is community-dwelling adults aged 40 years and older, who are not currently on pharmacotherapy to prevent fragility fractures.
5. Do you have any comments or suggestions to improve the guideline?	1. As written, the recommendations appear to the reader as applying to all individuals over the age of 40 and do not identify the actual patient group which is healthy, low risk men and women.	1. After discussion with the Task Force we have decided that the scope of this guideline should include all individuals regardless of risk. This decision was reached due to the difficulty in defining and operationalizing "high risk", and also the fact that these high risk factors (e.g., prior fracture, secondary osteoporosis, parental hip fracture, glucocorticoids) are all part of the FRAX calculation. Therefore, "high risk" can be determined using the FRAX tool as part of the "risk assessment-first" screening process. We also looked at the populations of the 3 main screening trials (SCOOP, ROSE, SALT) and the majority included these high risk populations as a proportion of their screening population. Additionally, those at elevated risk can still benefit from having a shared-decision making conversation with their primary care physician in the context of their calculated elevated risk. Therefore, the guideline can be applied to all individuals other than those already being treated with pharmacotherapy to prevent fragility fractures. We have changed the abstract, recommendations and scope sections to state: The target population for this guideline is community-dwelling adults aged 40 years and older, who are not currently on pharmacotherapy to prevent fragility fractures.
	2. The document comes across as minimizing the value of screening. We would suggest that clinical screening is very important in determining which individuals should go forward for DEXA. This is not clear in the guidelines	2. We agree that clinical screening is very important for females >=65 years. Unfortunately, there were no studies of "risk assessment-first" screening in men (any age) or women <65 years. Additionally there was no evidence of a benefit for men (≥65 years) when using DXA alone. When looking at calibration of FRAX, we used data for females and males separately in the analysis and there were 2 cohorts of each

		but combined the data since any heterogeneity was not explained by sex. Further, none of the subgroup analyses across all studies were significant for sex. We have tried to clarify clinical vs DXA screening by re-naming the process as "risk assessment-first" screening and describing the process in comparison to the "BMD-first" screening. "Risk assessment-first" screening includes fracture risk estimation (e.g., FRAX without BMD), followed (if indicated) by BMD. Risk is then re-estimated by adding the BMD T-score to the calculation. "Bone mineral density test-first" screening starts with BMD, usually followed by risk assessment. For both strategies, preventive pharmacotherapy may be offered to those identified as being at high fracture risk. We also clarified in the recommendation: • We recommend risk assessment-first screening to prevent fragility fractures in females aged 65 years and older as follows (conditional recommendation, low-certainty evidence): • FRAX: Apply the Canadian clinical FRAX risk assessment tool (without BMD). Use the 10-year absolute risk of MOFs to facilitate shared decision-making about the possible benefits and harms of preventive pharmacotherapy. • BMD + FRAX: After this discussion, if preventive pharmacotherapy is considered, request BMD measurement using DXA of the femoral neck. Then re-estimate fracture risk by adding the BMD T-score into FRAX.
	3. There is lack of clarity re clinical screening and DEXA screening in much of the text. There appear to be some errors, likely just typographical. (lines 143 to 149) "Preventive treatment" appears to be used as synonymous with pharmacotherapy which is likely to be	3. See above for clarifying clinical screening vs DEXA. We have clarified as follows: Lines 143-149: Zoledronic acid probably increases several non-serious AEs (e.g. ~~pyrexia,~~ headache, influenza-like symptoms, arthritis and arthralgia)~~, myalgia and the composite outcome "any non-serious AE"~~ (moderate certainty evidence) (21). Alendronate and bisphosphonates (as a drug class) ~~and alendronate~~ may increase rare but serious harms of atypical femoral fracture and osteonecrosis of

	confusing to the reader, since preventative therapy is often just calcium and vitamin D.	the jaw (low certainty evidence) (21). No other serious or non-serious AEs were associated with treatment. We have changed “preventive treatment” to “preventive pharmacotherapy” throughout the text

Reviewer 05 (Peer reviewer): David Goltzman, McGill University

Disclosure(s): None

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes	Thank you
3. Are the guidelines supported by the evidence?	In restricting BMD measurements to those with a high clinical FRAX score, the assumption is that BMD will then add to the use of FRAX alone, but only if clinical FRAX scores are already high. How many high risk individual will be missed by not screening with FRAX plus BMD at the outset. How many individuals will have high clinical FRAX risk scores and then normal or non-osteoporotic T-scores?	The task force decided not to put a clinical FRAX score threshold due to substantial variation seen in patient values and preferences. Therefore, access to BMD wouldn’t be limited to only those with a high clinical FRAX score. It would instead be a shared decision between the doctor and patient based on their preferences for treatment. Examples of baseline risk and individual risk will be available in an interactive decision aid tool being developed by the Task Force (Fragility Fracture Decision Aid (canadiantaskforce.ca). Additionally, although we did not look at data of direct comparisons between clinical FRAX vs. FRAX (w/BMD) but it appears (from low risk of bias Canadian studies) that FRAX with BMD may

		underestimate actual/observed risk somewhat more than clinical FRAX, such that the predicted/estimated risk (told to patient) would be lower from this tool vs the clinical FRAX.
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Raloxifene, Teriparatide and biosimilars, and Romosozumab have all been approved for use in osteoporosis. Should these be mentioned in the guidelines? Oral bisphosphonates, zoledronic acid and denosumab are all recommended for use with calcium and vitamin D(although RCTs have used varying doses)—should this be mentioned in the guidelines?	We decided to focus only on first-line bisphosphonates and denosumab as the other drugs are often used for very high risk patients (e.g. teriparatide, biosimilars, romosozumab) or less commonly used (raloxifene). The main focus of the guideline is on screening adults not previously identified as at elevated risk of fracture. Therefore, we don't make any treatment recommendations and focus on drugs that would be used in a screening population. We agree that calcium and vitamin D are recommended for use with bisphosphonates and denosumab. In most treatment studies vitamin D and calcium were given to <u>both</u> the treatment and the control arms. We have added a footnote to the tables to state that "Vitamin D and calcium were usually given as part of treatment to both cases and controls". We have also specified "Pharmacotherapy" instead of just "treatment" as the focus was on bisphosphonates or denosumab and not vitamin D + calcium.
5. Do you have any comments or suggestions to improve the guideline?	Please see my comments above. Overall, this has been a helpful exercise.	Thank you

Reviewer 06 (Peer reviewer): David Hogan, University of Calgary

Disclosure(s): Member of World Falls Guideline steering committee, received funding from CIHR, PHAC and the Canadian Foundation for Innovation for unrelated projects

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	1. The objective is not explicitly stated in the document. I assume it is to provide recommendations on screening to prevent fragility fractures in adults 40+. relatively clear but I do have some concerns/ questions.	1. After discussion with the Task Force we have decided that the scope of this guideline should include all individuals regardless of risk. This decision was reached due to the difficulty in defining and operationalizing "high risk", and also the fact that these high risk factors (e.g., prior fracture, secondary osteoporosis, parental hip fracture, glucocorticoids) are all part of the FRAX calculation. Therefore, "high risk" can be determined using the FRAX tool as part of the "risk assessment-first" screening process. We also looked at the populations of the 3 main screening trials (SCOOP, ROSE, SALT) and the majority included these high risk populations as a proportion of their screening population. Additionally, those at elevated risk can still benefit from having a shared-decision making conversation with their primary care physician in the context of their calculated elevated risk. Therefore, the guideline can be applied to all individuals other than those already being treated with pharmacotherapy to prevent fragility fractures. We have changed the abstract, recommendations and scope sections to state: The target population for this guideline is community-dwelling adults aged 40 years and older,

	2. First, while a lower age threshold is given there is no upper age limit for screening. Presumably this is because the risk of fractures continues to remain high if not continue to increase with increasing age after 65, and the risk of harm from treatment does not increase with age. As far as I know, the second contention is correct, but when life expectancy becomes a very limited period of time (e.g., year or less), the value of screening must surely be suspect. A very limited life expectancy is not solely linked to advanced age, but from whatever cause it does suggest to me there are other limitations to the recommendation of screening with the intent of potentially treating the older adult other than "…not known to be at elevated fracture risk and not on treatment to prevent fragility fractures" (see - https://www.meded101.com/starting-bisphosphonates-in-patients-with-limited-life-expectancy/). I don't think mention of "cancer" in those who are not included in the recommendation is sufficient (see below).	who are not currently on pharmacotherapy to prevent fragility fractures. 2. In regards to an upper age limit, we were unable to find any literature specifically analyzing when to stop screening. This is mentioned in the Gaps in Knowledge section "Evidence on screening frequency and at what age to stop is lacking". The risk of fracture does indeed increase with age, however, this should be weighed against other comorbidities and life expectancy when deciding to stop screening. Thank you for the article on bisphosphate use in patients with limited life expectancy. We have added to the Considerations for Implementation section: "We found no RCTs on screening intervals or age limits … Comorbidities and life expectancy should be considered for age limits and rescreening.
2. Are the patient groups to whom the guideline is meant to apply clearly described?	1. But there is a catch-22. The target group is "community dwelling adults aged ≥ 40 years who are not known to be at elevated fracture risk and not on treatment to prevent fragility fractures." It is later stated (in itilacs after the recommendations) that "do not apply to individuals at elevated risk due to previous fragility fracture diagnosis, endocrine or other disorders related to metabolic bone disease, cancer, chronic glucocorticoid use." The problem is that risk factors for osteoporotic fractures listed in the FRAX include these bolded	1. After discussion with the Task Force we have decided that the scope of this guideline should include all individuals regardless of risk. This decision was reached due to the difficulty in defining and operationalizing "high risk", and also the fact that these high risk factors (e.g., prior fracture, secondary osteoporosis, parental hip fracture, glucocorticoids) are all part of the FRAX calculation. Therefore, "high risk" can be determined using the FRAX tool as part of

	conditions - previous spontaneous or fragility fracture (see - Adachi, J.D., et al. Fragility fracture identifies patients at imminent risk for subsequent fracture: real-world retrospective database study in Ontario, Canada. BMC Musculoskelet Disord 2021, 22: 224), use of glucosteroids, and secondary osteoporosis (including a variety of endocrine and other causes). In other words a number of the states/ conditions that are included in the recommended screening tool (FRAX) would by there very presence have excluded those in the target population from being screened. Their removal plus sex (as FRAX is only being recommended for women) and DXA result would mean that the "revised" FRAX being used would be eseentially based on only 7 items and not, I'm pretty sure, validated. Possibly this could be helped by moving the italicized section up to the scope paragraph but it is hard to square the circle.	the "risk assessment-first" screening process. We also looked at the populations of the 3 main screening trials (SCOOP, ROSE, SALT) and the majority included these high risk populations as a proportion of their screening population. Additionally, those at elevated risk can still benefit from having a shared-decision making conversation with their primary care physician in the context of their calculated elevated risk. Therefore, the guideline can be applied to all individuals other than those already being treated with pharmacotherapy to prevent fragility fractures. We have changed the abstract, recommendations and scope sections to state: The target population for this guideline is community-dwelling adults aged 40 years and older, who are not currently on pharmacotherapy to prevent fragility fractures.
3. Are the guidelines supported by the evidence?	1. I wonder if in addition to the groups listed there should be mention that these recommendations do not apply to adults living in institutional settings. I realize that in the scope paragraph it is noted that these recommendations are for those residing in the community.	1. We have added this to the abstract: These recommendations apply to **community-dwelling individuals** who are not currently on pharmacotherapy to prevent fragility fractures.
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	1. First, would be screening done only once or at certain intervals?	1. We did not find any RCTs comparing screening intervals during our systematic review (we state "*No evidence was found for females aged 55-64, males aged 40-64 years or on screening intervals*."

		However, in the "Considerations for implementation" we state that: *We found no RCTs on screening intervals or age limits. Although some observational studies suggest intervals based on age, baseline BMD or absolute fracture risk, repeating BMD at 3-8 years did not improve fracture risk prediction (13,38–41).* We also added: *It is unknown how often to rescreen eligible females; however, rescreening within 8 years does not appear useful.*
	2. Second, there are other radiological methods (e.g., quantitative ultrasound) that can be used to screen for osteoporosis though I agree DXA is by far the modality most commonly used.	2. In terms of other radiological methods (e.g. quantitative ultrasound) the task force identified DXA a priori as the only modality under consideration as it is most commonly used in population screening in Canada and is considered the gold standard. This exclusion criteria can be seen in our protocol (https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-019-1094-5)
	3. Third, after finding an individual is at a sufficiently high risk for a fragility fracture that treatment is being considered, shouldn't there be an assessment for secondary/ contributing causes?	3. We agree that there should be an assessment for secondary causes following a high fracture risk score. However, the task force doesn't make recommendations beyond the screening intervention (i.e., no recommendations on diagnostic tests or treatment). However, we do talk about "secondary osteoporosis" briefly in the introduction. "Some disorders (e.g., diabetes and other endocrine disorders, rheumatoid arthritis, end-stage renal disease) or medications (e.g., chronic glucocorticoids)

		negatively affect bone density (often referred to as secondary osteoporosis) and increase the risk of fragility fracture." 4. We have added to the introduction that: Other interventions - such as exercise, smoking cessation, fall prevention strategies and adequate calcium and vitamin D intake - may also reduce risk. However, the focus of this guideline was on the prevention of fragility fractures through screening and pharmacotherapy. The Task Force will be issuing a separate guideline on Falls and may look at the other topics separately as well. We have also added to the background: This Canadian Task Force on Preventive Health Care (task force) guideline provides evidence-based recommendations on screening, focusing on the primary prevention of fragility fractures through pharmacotherapy. A separate task force guideline on falls prevention is underway. And to the scope: Recommendations on treatment and non-pharmacological prevention are not included. 5. We decided to focus only on first-line treatments and denosumab (often used if contraindications to bisphosphonates) as the other drugs are often used for high risk patients (e.g. teriparatide, biosimilars, romosozumab) or
	4. Fourth, I feel there should be more attention placed on the potential of non-pharmacological interventions (e.g., fall prevention, physical activity/exercise, diet, calcium/ vitamin D, abstain from alcohol and smoking – see: https://www.canada.ca/en/public-health/services/chronic-diseases/osteoporosis.html). 5. Fifth, there are other forms of pharmacological interventions available in Canada for osteoporosis in addition to the current focus on bisphosphonates and denosumab (see - https://osteoporosis.ca/treatment/ and https://osteoporosis.ca/romosozumab/).	

	6. Finally, no mention was made of Fracture Liaison Services, which do have a role in identifying fragility fractures and implementing therapy in hospitalized patients (see - https://fls.osteoporosis.ca/what-is-fls/). I think they should be noted if only to say they will not be dealt with.	less commonly used (raloxifene). The main focus of the guideline is on screening therefore, we wanted to focus on drugs that would be used in a screening population. 6. The focus of this guideline was on primary prevention through screening. However, we have added that "Clinicians should also be aware of the importance of secondary prevention (i.e., after fracture) and manage patients accordingly."
5. Do you have any comments or suggestions to improve the guideline?	Nothing further.	Thank you

Reviewer 07 (Peer reviewer): Dr. Ingeborg Schabort, McMaster University

Disclosure(s): None

Question	Reviewer comments	CTFPHC response
1. Is the objective of the guideline clear?	Yes	Thank you
2. Are the patient groups to whom the guideline is meant to apply clearly described?	Yes	Thank you
3. Are the guidelines supported by the evidence?	Yes	Thank you
4. Is there any information missing from the guideline that would make it easier to interpret for primary care practitioners?	Yes (see question 5 below)	(See below)
5. Do you have any comments or suggestions to improve the guideline?	1. When you state ”These recommendations do not apply to individuals at elevated risk of fragility fractures due to previous diagnosis of fragility fracture, endocrine or other disorders likely to be related to metabolic bone disease, cancer, chronic use of glucocorticoid medications, or those currently on treatment to prevent fragility fractures.” You would have to be more explicit with primary care providers re what you include here eg steroid dosing for how long etc-as in the osteoporosis.ca guidelines.	1. After discussion with the Task Force we have decided that the scope of this guideline should include all individuals regardless of risk. This decision was reached due to the difficulty in defining and operationalizing "high risk", and also the fact that these high risk factors (e.g., prior fracture, secondary osteoporosis, parental hip fracture, glucocorticoids) are all part of the FRAX calculation. Therefore, "high risk" can be determined using the FRAX tool as part of the “risk assessment-first” screening process. We also looked at the populations of the 3 main screening trials (SCOOP, ROSE, SALT) and the majority included these high risk populations as a proportion of their screening population. Additionally, those at elevated risk can still benefit from having a shared-decision making conversation

		with their primary care physician in the context of their calculated elevated risk. Therefore, the guideline can be applied to all individuals other than those already being treated with pharmacotherapy to prevent fragility fractures. We have changed the abstract, recommendations and scope sections to state: The target population for this guideline is community-dwelling adults aged 40 years and older, who are not currently on pharmacotherapy to prevent fragility fractures.
	2. I see the comments on potential cost savings, but it is not clear to me whether the cost of BMD was taken into account when making your final recommendation. You would need to be more explicit re this aspect.	2. The cost of BMD (as well as medication, physician time and cost for hip surgery, hospitalization, etc.) was taken into account and is mentioned in the Evidence to Decision framework (Appendix 10, pg 61-63). We have added a reference to Appendix 10 to the section on resource use
	3. I may have missed this, but I did not see whether you mean one time screening or with what intervals this process needs to be repeated.	3. The guideline states: We found no RCTs on screening intervals or age limits. Although some observational studies suggest intervals based on age, baseline BMD or absolute fracture risk, repeating BMD at 3-8 years did not improve fracture risk prediction. It is unknown how often to rescreen eligible females; however, rescreening within 8 years does not appear useful. Comorbidities and life expectancy should be considered for age limits and rescreening.
	4. I anticipate confusion amongst primary care providers regarding not screening men 40 and	4. We did not find any evidence for males <65 years and the evidence for males >=65 years was very uncertain and did not show a significant benefit of

	over, due to the osteoporosis.ca guidelines that would conflict on screening men 65 and over. I would think you would need to be more explicit about the 65 and above male group in addition to the 40 and over	screening. Therefore, we strongly recommend against screening for both groups of males. We understand that this is different from the Osteoporosis Canada recommendations and have mentioned that in the section on Other Guidelines (i.e. "we recommend risk assessment-first while the Osteoporosis Canada 2010 guideline recommends BMD testing first, followed by risk assessment. The 2010 Osteoporosis Canada guideline recommends informal risk assessment-first screening (based on a list of risk factors) for males and females aged 50-64 years (information was unavailable for their upcoming guideline). We recommend against screening males aged 40 years and older, whereas Osteoporosis Canada recommends BMD testing-first screening for males aged 70 years and older".) We will be using our Knowledge Translation materials (e.g. FAQs, clinician summary, etc.) to help answer questions stakeholders may have about the differences between our guideline and Osteoporosis Canada's.