Evidence-to-Recommendation Framework

This document outlines the underpinning evidence and rationale for the recommendations in the ACE Clinical Guideline (ACG) "Osteoporosis: diagnosis and management".

In ACGs, the strength of a recommendation reflects the confidence that the desirable effects of the recommended practice outweigh undesirable effects across the range of patients for whom the recommendation applies, based on the best available evidence:

- A strong recommendation is usually made when benefits clearly outweigh the risks, based on at least moderate-certainty evidence.
- A weak or conditional recommendation may be needed when there is a closer balance between benefits and harms, evidence is of low certainty, there is significant variability in patients' values and preferences, or important concerns with resourcing and feasibility of the recommended practice.[1]

Recommendation 1	**Determine the need for bone mineral density testing in people with risk factors for osteoporosis or fragility fractures, particularly all postmenopausal women, and men ≥ 65 years of age.**

Strength of recommendation: Strong | Weak / conditional

Summary:

The Expert Group agreed on a strong recommendation based on high-certainty evidence (particularly for the association between age, menopausal status and risk of osteoporosis) and feasibility considerations. The recommendation supports current practice, aligns with local trends, and expert consensus on targeting individuals most likely to benefit from timely assessment, while considering resource implications.

Balance of benefits and harms	**Values and preferences**
Identifying individuals with clinical risk factors for osteoporosis or fragility fractures is essential to prioritise those who may benefit from BMD testing and early intervention. International guidelines consistently recommend risk assessment in all postmenopausal women, and some extend this recommendation to older men, although the specific age cut-offs vary. Postmenopausal Women: American guidelines such as that of United States Preventive Services Task Force (USPSTF), American College of Physicians (ACP), American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACOE) and American College of Obstetricians and Gynecologists (ACOG) recommend osteoporosis screening for all women aged ≥65 years, and for younger postmenopausal women with at least one clinical risk factor.[2-6] Canadian, UK (Scottish Intercollegiate Guidelines Network (SIGN), National Osteoporosis Guideline Group (NOGG)), and Malaysian guidelines adopt a risk-based approach but still prioritise assessment from age 65 or 70 years in postmenopausal women with no additional risk factors.[7-11] Men: Most international guidelines do not recommend routine assessment in men. ACP, SIGN and NOGG support risk-based evaluation, particularly in men ≥70 years or younger	Variability in patients' values/preferences for osteoporosis risk assessment is not expected. Visual tools and clear communication (e.g. risk charts) help support informed decisions and are preferred over vague explanations.[13]

men with significant risk factors (e.g. prior fracture, chronic steroid use, hypogonadism).[3,9,10] The Malaysian guideline similarly recommends BMD screening in men ≥70 years, or earlier if risk factors are present, aligning with the Endocrine Society, International Society for Clinical Densitometry (ISCD), and supplements this stance with national data.[11] USPSTF and Canadian guidelines conclude that evidence is insufficient to recommend routine screening in men.[2,7,8] Local Context: In Singapore, data from 2012 to 2022 show that the incidence of hip fracture-related hospitalisations and non-hip fracture-related healthcare visits in men increases progressively with age.[12] Although men have lower absolute fracture risk than women, the comparable age-related risk trajectory supports early detection. Adapting the threshold for clinical assessment to age 65 years allows clinicians to identify at-risk men earlier, enabling timely intervention and prevention of fragility fractures.	
Certainty of evidence	**Resource use and feasibility**
There is high certainty that age and menopausal status are major risk factors for osteoporosis and fragility fractures. While international recommendations for men vary in age cut-offs or acknowledge the lack of data to justify blanket recommendations, the biological plausibility of age-related bone loss is well established.	Recommending clinical assessment in postmenopausal women and using age 65 years for men aligns with current protocols in primary care clinics, supporting continuity of care and minimising disruption. A lower age cut off for men could substantially increase the number of men needing risk assessment and possibly BMD testing, posing high burden on the system with unclear benefit given the lower incidence of osteoporosis and/or fragility fractures in younger men.
Expert Group deliberation of above factors	
The Expert Group discussed the evidence presented and recommended risk-based assessment in postmenopausal women and in men from age 65. For men, while direct evidence supporting routine assessment is limited, the Expert Group noted that the age-related increase in fracture incidence and international guideline precedents justify a pragmatic threshold of 65 years in the local context, without overburdening healthcare resources. Additionally, the Expert Group supported ongoing clinical discretion to assess men aged <65 years with risk factors such as chronic steroid use, hypogonadism, or significant comorbidities.	

Recommendation 2	**Optimise lifestyle management for all patients at risk of osteoporosis or fragility fractures, including calcium and vitamin D intake through diet and supplementation as appropriate.**

Strength of recommendation: Strong | Weak / conditional

Summary:

The Expert Group agreed that while adequate calcium and vitamin D intake is important across the life course, it is especially critical for those at increased risk, such as postmenopausal women and older men. In Singapore, dietary calcium intake remains suboptimal and vitamin D insufficiency is common. Guidelines agree that optimising these and other modifiable factors supports bone health and reduces fracture risk, forming a core pillar of preventive care.

Balance of benefits and harms	Values and preferences
Lifestyle interventions such as adequate calcium and vitamin D intake (and supplementation when needed), physical activity, fall prevention, smoking cessation, and limiting alcohol intake are widely recommended in international guidelines.[2,4,5,8-11] Although variation exists in the recommended sources and doses of calcium and vitamin D, all guidelines endorse ensuring sufficient intake. In Singapore, the average daily calcium intake (794 mg) is under the recommended daily allowance of 1,000–1,200 mg/day, and local studies report vitamin D insufficiency in 42–92% of individuals.[14-17] Targeting these deficiencies, particularly among at-risk individuals, is important for fracture prevention. The local context also supports the use of supplementation when dietary intake is inadequate and includes vitamin D loading in selected situations (e.g. prior to initiation of denosumab).	Patients consistently value lifestyle-based strategies, such as improving calcium and vitamin D intake, engaging in physical activity, reducing alcohol intake and preventing falls, especially in the early stages of osteoporosis care.[18-20] These measures are seen as practical, non-invasive, and within the patient's control. There is also a preference for tailored, culturally relevant guidance that aligns with individual habits, beliefs, and functional status. Notably, goal-setting has been shown to increase patient engagement and improve health outcomes, making it a useful preventive strategy when counselling individuals at risk of osteoporosis.[20]
Certainty of evidence	**Resource use and feasibility**
Although direct evidence linking lifestyle measures to fracture reduction is limited, the cumulative body of evidence and biological plausibility strongly support their role in bone health.[21] There is moderate certainty supporting vitamin D supplementation, due to mixed evidence in reducing fall and fracture risk among older adults. The evidence for calcium supplementation is of moderate certainty, with modest benefit on bone metabolism when combined with vitamin D, especially in those with low dietary intake. While guideline thresholds vary, there is general agreement on the utility of supplementation in high-risk groups.	Lifestyle optimisation is highly feasible and cost-effective in primary care settings. Dietary advice, exercise promotion, fall prevention, and patient education are already part of routine practice. Supplements such as calcium and vitamin D are widely available. Laboratory testing (e.g. 25(OH)D) may be costly in some settings, but targeted testing approaches ensure reasonable access and minimise out-of-pocket costs for patients. Education materials and decision tools (e.g. calcium calculator) can further support implementation.
Expert Group deliberation of above factors	
The Expert Group unanimously supported this strong recommendation, affirming the importance of lifestyle management, including calcium and vitamin D optimisation, for all individuals at risk of osteoporosis or fragility fractures. The word "optimise" was intentionally used to reflect the need for personalised advice based on individual lifestyle and risk profiles. The Expert Group prioritised the mention of "calcium and vitamin D intake" due to persistently low intake and high insufficiency rates in Singapore. A daily maintenance dose of 1,000 IU vitamin D was endorsed, while loading and repeat testing were reserved for select cases based on clinical need and resource considerations.	

Recommendation 3	**a) Diagnose osteoporosis and initiate treatment for patients with current or past fragility fracture, or a BMD (measured by central DXA) T-score ≤ –2.5.** **b) Consider initiating treatment for people with a BMD (measured by central DXA) T-score between –1.0 and –2.5 at high risk of fractures.**

Strength of recommendation:

a)	**Strong**	Weak / conditional
b)	Strong	**Weak / conditional**

Summary:

The Expert Group agreed on a strong recommendation to diagnose and treat osteoporosis in individuals with a fragility fracture or a Dual-energy X-ray Absorptiometry (DXA)-measured BMD T-score ≤ –2.5, as these criteria align with WHO definitions and international clinical guidelines. Due to a closer balance

between benefits and harms, as well as lower certainty of evidence, the Expert Group agreed on a conditional recommendation for treatment in individuals with BMD between –1.0 and –2.5 who are at high fracture risk. While this reflects growing recognition of the need to prevent fractures in high-risk individuals even if they do not meet the strict diagnostic threshold for osteoporosis, it enables a greater degree of individualisation based on patient's fracture risk and needs.

Balance of benefits and harms	**Values and preferences**
There is strong consensus across international guidelines that individuals with a fragility fracture or BMD T-score ≤ –2.5 should be diagnosed with osteoporosis and offered treatment, as these factors are associated with significantly increased fracture risk.[2,4,9-11] Initiating treatment in these groups helps prevent future fractures and associated morbidity. For individuals with BMD between –1.0 and –2.5, there is closer balance between benefits and harms and treatment decisions should be guided by overall fracture risk rather than BMD alone. While direct trial evidence for this group is limited, observational studies have shown that a substantial proportion of fractures occur in patients with low bone mass.[22] The use of a risk-based approach allows for more precise identification of those likely to benefit from treatment. In Singapore, local thresholds developed through in-house cost-effectiveness modelling provide an evidence-informed and pragmatic basis to guide treatment initiation in this group.	Patients with or at high risk of osteoporosis prioritise treatment efficacy but also consider administration mode, side effects, and cost. A recent systematic review showed many are willing to trade off these factors, underscoring the importance of shared decision-making.[24] There is also substantial preference heterogeneity, reinforcing the need to individualise treatment plans.[24] Aligning therapy with patient preferences may improve adherence and outcomes, especially in borderline cases where clinical factors other than BMD confer risk, and patient motivation is key.
Certainty of evidence	**Resource use and feasibility**
There is high certainty supporting the benefits of initiating treatment in individuals with an established diagnosis of osteoporosis. Multiple large-scale RCTs and systematic reviews cited in international guidelines have demonstrated reductions in fracture risk with pharmacologic treatment in these groups.[4,5,8-11] For individuals with BMD between –1.0 and –2.5 (low bone mass), there is low certainty evidence, particularly due to the limited number of RCTs focused specifically on this subgroup. The 2023 systematic review by the ACP identified only two RCTs evaluating treatment in patients with osteopenia.[23]	The use of central DXA for diagnosing osteoporosis is widely accepted and already available in Singapore, although access may vary across settings. Clinical risk assessment tools such as FRAX® are freely accessible online, making them feasible for routine use in primary care. Applying locally derived cost-effectiveness thresholds helps guide treatment decisions in patients with low bone mass, supporting resource-efficient care without compromising clinical outcomes (refer to the supplementary material 'Methodology used for economic evaluation of intervention thresholds for patients with osteopenia' for the evidence and Expert Group deliberations underpinning the recommended thresholds).
Expert Group deliberation of above factors	
The Expert Group strongly endorsed initiating treatment for individuals with osteoporosis, given the clear evidence of benefit. For those with low bone mass, the Expert Group supported a risk-based approach, aligning with ACE's locally modelled treatment thresholds to balance under- and over-treatment. The Expert Group emphasised the importance of flexibility in applying the recommendations. They recognised that BMD and fracture risk may not always align, and clinicians should be supported to exercise judgement in such scenarios, particularly in settings with limited access to DXA.	

Recommendation 4	**For patients in whom pharmacological treatment is indicated:** • **Use oral alendronate or risedronate (or IV zoledronate if available and preferred)** • **Consider using denosumab, if preferred and suitable for the patient.**

Strength of recommendation:

- Bisphosphonates — **Strong** | Weak / conditional
- Denosumab — Strong | **Weak / conditional**

Summary of rationale

The Expert Group agreed on a strong recommendation to use oral alendronate or risedronate, or IV zoledronate if preferred, as first-line pharmacological treatment in patients with osteoporosis or at high risk of fracture. These agents are widely endorsed in international guidelines due to robust evidence of fracture risk reduction across vertebral, non-vertebral, and hip sites, and have established availability and cost-effectiveness in Singapore. The Group supported a weaker recommendation for denosumab, acknowledging its similar efficacy but recognising potential risks upon discontinuation, higher cost, and logistical constraints in primary care.

Balance of benefits and harms	**Values and preferences**
Oral alendronate, risedronate, and IV zoledronate have been shown to reduce the risk of vertebral, non-vertebral, and hip fractures.[3,4,26-28] Gastrointestinal side effects (oral) and acute phase reactions (IV) are common and typically mild. Denosumab offers comparable efficacy but carries unique risks.[4,6,11,25] Rebound vertebral fractures can occur with missed doses or abrupt discontinuation, especially without timely transition to another agent.[29] However, denosumab remains a viable option for patients with renal impairment (creatinine clearance <30 mL/minute), where bisphosphonates may be contraindicated. Denosumab may also be appropriate for patients unable to tolerate or comply with bisphosphonate therapy, or who prefer the subcutaneous route. Severe adverse effects such as medication-related osteonecrosis of the jaw (MRONJ) and atypical femoral fractures (AFF) are extremely rare, especially in the first 3 to 5 years of treatment.[30-32] For patients on long-term bisphosphonate therapy, a drug holiday may be considered to minimise rare adverse effects while retaining residual fracture protection.[33]	Patients place high value on treatments that reduce fracture risk, but they also strongly consider the mode and frequency of administration, risk of side effects, and out-of-pocket costs when choosing osteoporosis therapy.[24,34] Subcutaneous injections every six months and monthly oral tablets are generally preferred over weekly tablets or intravenous infusions.[35] However, preferences vary widely across individuals, and some patients may opt for IV formulations or daily pills if these align better with their lifestyle or perceptions of efficacy.[24] Tailoring treatment options with individual preferences is essential to improve adherence and achieve optimal outcomes.
Certainty of evidence	**Resource use and feasibility**
There is high-certainty evidence supporting the use of oral alendronate, risedronate, and IV zoledronate as first-line agents for the treatment of osteoporosis. Multiple large-scale RCTs and systematic reviews have demonstrated risk reduction of vertebral, non-vertebral, and hip fractures in postmenopausal women and older men.[26-28] For denosumab, there is high-certainty evidence. Several RCTs and meta-analyses have shown comparable efficacy to bisphosphonates. However, concerns about rebound vertebral fractures upon discontinuation lower confidence in long-term outcome.[26-29]	Oral bisphosphonates (alendronate, risedronate) are low-cost generics listed on the MOH subsidised drug list and Healthier SG medication list, making them the most accessible and affordable option in primary care. IV zoledronate and denosumab are both subsidised under the MOH drug list but are not included in the Healthier SG medication list. IV zoledronate is less feasible in primary care due to infusion requirements and limited availability outside tertiary institutions. Denosumab requires cold chain storage and strict adherence to 6-monthly dosing, which

	may pose logistical challenges in some settings.
Expert Group deliberation of above factors	
The Expert Group supported a recommendation for pharmacological management that reflected differentiated options based on feasibility, patient suitability, and implementation considerations. While bisphosphonates remain the preferred first-line agents, the group acknowledged that denosumab may be the most suitable option for selected patients, such as those with renal impairment or adherence challenges.	

Recommendation 5	**Consider anabolic agents as first-line treatment for patients at very high risk of fractures, with specialist input as needed.**

Strength of recommendation: Strong | **Weak / conditional**

Summary:

The Expert Group conditionally recommended anabolic agents (teriparatide, romosozumab) as first-line treatment in patients at very high risk (VHR) of fractures, based on evidence of superior vertebral fracture risk reduction compared to bisphosphonates. This reflects international guideline trends, although the benefit for non-vertebral fractures is less certain as compared to antiresorptive therapies. Due to limited evidence clearly defining which patients should receive anabolic agents, the recommendation was worded with "consider" and proposed VHR criteria are outlined in the supporting text to guide prescribing practices.

Balance of benefits and harms	**Values and preferences**
In VHR patients, teriparatide has been shown to reduce vertebral fracture rates by 31–59% more than oral bisphosphonates, while romosozumab achieves an approximately two-fold reduction.[36-40] Both agents also reduce non-vertebral fracture risk, but their effectiveness is comparable to bisphosphonates, with no clear evidence of additional benefit. Both agents should be followed by antiresorptive therapy to preserve gains in bone mineral density and prevent rebound bone loss.[3,4,6,9-11] Common side effects of teriparatide include nausea, dizziness, leg cramps, and transient hypercalcaemia.[3,4,6,9-11,23] Previous restrictions on duration of use have recently been lifted by the US Food and Drug Administration (FDA).[41] Romosozumab may cause hypocalcaemia especially in patients with renal impairment and is contraindicated in individuals with previous myocardial infarction or stroke, due to increased cardiovascular risk.[3,4,6,9-11,23]	Teriparatide requires daily subcutaneous injections, while romosozumab is administered monthly, making the latter potentially more acceptable to patients.[24] However, romosozumab is only approved for use in postmenopausal women, meaning VHR men would need to be treated with teriparatide if anabolic therapy was indicated. Tailoring treatment options with individual preferences is essential to improve adherence and achieve optimal outcomes.
Certainty of evidence	**Resource use and feasibility**
There is moderate-certainty evidence that anabolic agents such as teriparatide and romosozumab reduce vertebral fracture risk more effectively than oral bisphosphonates in patients at VHF of fractures.[36-40,42] Some international guidelines recommend anabolic agents as first-line treatment for patients at VHR, supporting their superior bone-forming mechanism and vertebral fracture reduction benefits in this subgroup.[3,4,10,25] However, the generalisability of trial data is limited, as most studies enrolled postmenopausal women without subgroup analyses of patients at VHR of fracture or severe osteoporosis.	Anabolic agents are more expensive than oral bisphosphonates and may pose affordability challenges for patients. Unlike romosozumab, teriparatide is subsidised under the MOH subsidised drug list for patients who meet the defined criteria for VHR of fractures (T-score ≤ –3.0 and ≥2 vertebral or fragility fractures). Both agents are not included in the Healthier SG medication list, limiting their accessibility in the private primary care setting.
Expert Group deliberation of above factors	

The Expert Group supported a standalone recommendation to highlight the role of anabolic agents in patients at VHR of fractures and to future-proof the ACG in anticipation of access to teriparatide in primary care settings in 2025 (which is currently limited to specialist use).

The Expert Group also noted that while the US FDA has removed the previous 2-year limitation on teriparatide use, a cautious approach should be taken. Prolonging treatment beyond 2 years should be considered only after re-evaluation and if the patient remains at VHR of fractures.

The wording of the recommendation was refined to clarify that anabolic agents may be considered *as first-line treatment* with appropriate context (i.e. patients with VHR of fractures), to avoid confusion with the general first-line option for all osteoporosis cases.

Recommendation 6	**Consider referring patients with clinically complex or unusual presentations to specialists for further assessment and management.**

Strength of recommendation: Strong | **Weak / conditional**

Summary:

The Expert Group agreed on a conditional recommendation for specialist referral for patients with clinically complex or unusual presentations. This includes those with potential secondary causes of osteoporosis, treatment-resistant cases, or specific physiological considerations. While these referrals align with existing guidelines and local primary care protocols, the recommendation was worded conditionally ("consider") due to variability in practice and the need for clinical judgment.

Balance of benefits and harms	**Values and preferences**
Specialist referral, as supported by various international guidelines is particularly important in cases where standard pharmacological treatment fails to prevent fractures or bone loss despite good adherence, or where patients present with suspected secondary osteoporosis.[8-10,25] These situations may require further investigation (e.g. laboratory testing, advanced imaging, or bone biopsy) and consideration of treatment options beyond the primary care formulary.	Patients commonly seek second opinions when facing diagnostic uncertainty or inadequate treatment response. Reassurance and increased trust in decisions are common motivations, even when initial care was appropriate.[43] While primary care plays a central role in osteoporosis management, collaborative ties with specialists with clear referral pathways can improve patient satisfaction, ensure timely access to specialist care and support shared decision-making.[44]
Certainty of evidence	**Resource use and feasibility**
Direct comparative trials on referral versus non-referral pathways are lacking. However, the inclusion of referral criteria in major osteoporosis guidelines reflects high consensus among expert panels. This consensus, combined with indirect evidence and pathophysiological rationale, supports a recommendation.	While specialist referrals can increase healthcare utilisation and costs, they can also improve care quality and enable timely initiation of advanced therapy. Clear referral criteria can optimise resource allocation and reduce variation in clinical practice. Local referral pathways already exist for primary care practitioners to refer patients needing specialist input.
Expert Group deliberation of above factors	
The Expert Group supported the addition of VHR of fracture as a criterion for specialist referral, aligning with Recommendation 5, particularly for primary care practitioners who may require specialist input to commence anabolic agents. The Expert Group also introduced two new criteria: pregnancy- and lactation-associated osteoporosis and perimenopausal women with osteoporosis or premature ovarian insufficiency/early menopause, to highlight clinical scenarios not previously addressed in the 2018 ACG but deemed important for appropriate specialist management.	

References

1. Schünemann H, Brożek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. [updated October 2013]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html#h.1yd7iwhn8pxp.
2. US Preventive Services Task Force. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. *JAMA* 2025; 333(6): 498–508.
3. Qaseem A, Forciea MA, McLean RM, Denberg TD. Pharmacologic treatment of primary osteoporosis or low bone mass to prevent fractures in adults: a clinical guideline update from the American College of Physicians. *Ann Intern Med* 2017; 166(11): 818–839.
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis—2020 Update. *Endocr Pract* 2020; 26(Suppl 1): 1–46.
5. American College of Obstetricians and Gynecologists (ACOG). Osteoporosis Prevention, Screening, and Diagnosis: ACOG Clinical Practice Guideline No. 1. *Obstet Gynecol* 2021; 138(3): 494–506.
6. American College of Obstetricians and Gynecologists (ACOG). Management of Postmenopausal Osteoporosis: ACOG Clinical Practice Guideline No. 2. *Obstet Gynecol* 2022; 139(4): 698–717.
7. Thériault G, Limburg H, Klarenbach S, et al. Recommendations on screening for primary prevention of fragility fractures. *CMAJ* 2023; 195(18): e639–e649.
8. Morin SN, Feldman S, Funnell L, et al. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. *CMAJ* 2023; 195(39): e1333–e1348.
9. Scottish Intercollegiate Guidelines Network (SIGN). Management of osteoporosis and the prevention of fragility fractures. Edinburgh: SIGN; 2021. (SIGN publication no. 142).
10. Gregson CL, Armstrong DJ, Bowden J, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos* 2022; 17(1): 58.
11. Ministry of Health Malaysia. Clinical practice guidelines: management of osteoporosis. 3rd ed. Malaysia: MOH; 2022.
12. Ministry of Health Singapore. Incidence of hip fracture-related hospitalisations and non-hip fracture-related healthcare visits in men and women from 2012 to 2022. Unpublished.
13. Edmonds SW, Cram P, Lu X, et al. Improving bone mineral density reporting to patients with an illustration of personal fracture risk. *BMC Med Inform Decis Mak* 2014; 14: 101.
14. Balk EM, Adam GP, Langberg VN, et al. Global dietary calcium intake among adults: a systematic review. *Osteoporos Int* 2017; 28(12): 3315–3324.
15. Bi X, Tey SL, Leong C, et al. Prevalence of Vitamin D Deficiency in Singapore: Its Implications to Cardiovascular Risk Factors. *PLoS One* 2016; 11(1): e0147616.
16. Neo JJ, Kong KH. Prevalence of Vitamin D Deficiency in Elderly Patients Admitted to an Inpatient Rehabilitation Unit in Tropical Singapore. *Rehabil Res Prac* 2016; 2016(1): 9689760.
17. Ramason R, Selvaganapathi N, Ismail NHB, et al. Prevalence of Vitamin D Deficiency in Patients With Hip Fracture Seen in an Orthogeriatric Service in Sunny Singapore. *Geriatr Orthop Surg Rehabil* 2014; 5: 82–86.
18. Beaudart C, Boonen A, Li N, et al. Patient preferences for lifestyle behaviours in osteoporotic fracture prevention: a cross-European discrete choice experiment. *Osteoporos Int* 2022; 33(6): 1335–1346.
19. Canals-Ruiz L, Comellas M, Lizán L. Preferences, satisfaction and decision-making processes in osteoporosis treatment: a systematic review of the literature. *J Comp Eff Res* 2021; 10(8): 591–607.
20. Prah A, Richards E, Griggs R, Simpson V. Enhancing osteoporosis efforts through lifestyle modifications and goal-setting techniques. *J Nurse Pract* 2017; 13(8): 552–561.
21. Wilson-Barnes SL, Lanham-New SA, Lambert H. Modifiable risk factors for bone health & fragility fractures. *Best Pract Res Clin Rheumatol* 2022; 36(3): 101758.
22. Reid IR, McClung MR. Osteopenia: a key target for fracture prevention. *Lancet Diabetes Endocrinol* 2024; 12(11): 856–864.

23. Ayers C, Kansagara D, Lazur B, et al. Effectiveness and Safety of Treatments to Prevent Fractures in People With Low Bone Mass or Primary Osteoporosis: A Living Systematic Review and Network Meta-analysis for the American College of Physicians. *Ann Intern Med* 2023; 176(2): 182–195.
24. Hinzpeter EL, Nagendra L, Kairies-Schwarz N, et al. Stated preferences of at-risk populations for the treatment of osteoporosis: a systematic review. *Patient* 2024; 17(6): 619–634.
25. Eastell R, Rosen CJ, Black DM, et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline. J *Clin Endocrinol Metab* 2019; 104(5): 1595–1622.
26. Barrionuevo P, Kapoor E, Asi N, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. *J Clin Endocrinol Metab* 2019; 104(5): 1623–1630.
27. Diez-Perez A, Adachi JD, Agnusdei D, et al. Treatment failure in osteoporosis. *Osteoporos Int* 2012; 23(12): 2769–2774.
28. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 2008; 148(3): 197–213.
29. Tsourdi E, Zillikens MC, Meier C, et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. *J Clin Endocrinol Metab* 2020; dgaa756.
30. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015; 30(1): 3–23.
31. Penoni DC, Canellas JVS, Silami MANC, et al. Osteonecrosis of the jaws in patients under osteoporosis treatment: a nine-year experience report. *Arch Endocrinol Metab* 2023; 67(4): e000612
32. Black DM, Geiger EJ, Eastell R, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med* 2020; 383(8): 743–753.
33. Hayes KN, Winter EM, Cadarette SM, et al. Duration of bisphosphonate drug holidays in osteoporosis patients: a narrative review of the evidence and considerations for decision-making. *J Clin Med* 2021; 10(5): 1140.
34. Duarte JW, Bolge SC, Sen SS. An evaluation of patients' preferences for osteoporosis medications and their attributes: the PREFER-International study. *Clin Ther* 2007; 29(3): 488–503.
35. Hiligsmann M, Dellaert BG, Dirksen CD, et al. Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. *Arthritis Res Ther* 2014; 16: R36.
36. Händel MN, Cardoso I, von Bülow C, et al. Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials. *BMJ* 2023; 381: e068033.
37. Huang W, Nagao M, Yonemoto N, et al. Evaluation of the efficacy and safety of romosozumab (evenity) for the treatment of osteoporotic vertebral compression fracture in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials (CDM-J). *Pharmacoepidemiol Drug Saf* 2023; 32(6): 671–684.
38. Shen J, Ke Z, Dong S, et al. Pharmacological Therapies for Osteoporosis: A Bayesian Network Meta-Analysis. *Med Sci Monit* 2022; 28: e935491.
39. Wang WY, Chen LH, Ma WJ, et al. Drug efficacy and safety of denosumab, teriparatide, zoledronic acid, and ibandronic acid for the treatment of postmenopausal osteoporosis: a network meta-analysis of randomized controlled trials. *Eur Rev Med Pharmacol Sci* 2023; 27(17): 8253–8268.
40. Wei FL, Gao QY, Zhu KL, et al. Efficacy and safety of pharmacologic therapies for prevention of osteoporotic vertebral fractures in postmenopausal women. *Heliyon* 2023; 9(2): e11880.
41. Krege JH, Gilsenan AW, Komacko JL et al. Teriparatide and osteosarcoma risk: History, science, elimination of boxed warning, and other label updates. *JBMR Plus* 2022; 6(9): e10665.
42. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017; 377(15): 1417–1427.

43. Greenfield G, Shmueli L, Harvey A, et al. Patient-initiated second medical consultations—patient characteristics and motivating factors, impact on care and satisfaction: a systematic review. *BMJ Open* 2021; 11(9): e044033.
44. Khatri P, Nastar A, Teng GG, Phua J. Re-examining the roles of generalists and specialists in healthcare. *Ann Acad Med Singap* 2023; 52(3): 149–153.