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Dr. Kendler graduated from the MD program at the University of Toronto in 1977. After completing a rotating internship in Toronto, he practiced for several years in Canada, Botswana, and New Zealand. He returned to Internal Medicine training in 1983 in Christchurch, New Zealand and in 1984 joined the Internal Medicine program in Halifax, Canada. In 1985 he moved to Vancouver to complete Internal Medicine and Endocrinology training at the University of British Columbia. After a 2-year thyroid immunology Fellowship in New York, he returned to the University of British Columbia Faculty of Medicine where he is now a Professor of Medicine in Endocrinology. He has led osteoporosis programs at Children and Women's Hospital and St. Paul's Hospital. He is the director of Prohealth Clinical Research, a major North American centre for clinical trials in the area of osteoporosis. He serves on the Scientific Advisory Council of Osteoporosis Canada and Chairs the Western Osteoporosis Alliance. He is a Past-President of the International Society for Clinical Densitometry. He is a member of the Committee of Scientific Advisors of the International Osteoporosis Foundation and is co-Chair of the Western Osteoporosis Alliance. He has been awarded the John Bilezekian ISCD Global Leadership Award and the IOF President's award. He has served on the Board of Directors of the Canadian Menopause Society. He has published over 140 peer-reviewed papers on osteoporosis therapies, osteoporosis risk assessment, and autoimmune thyroid disease.

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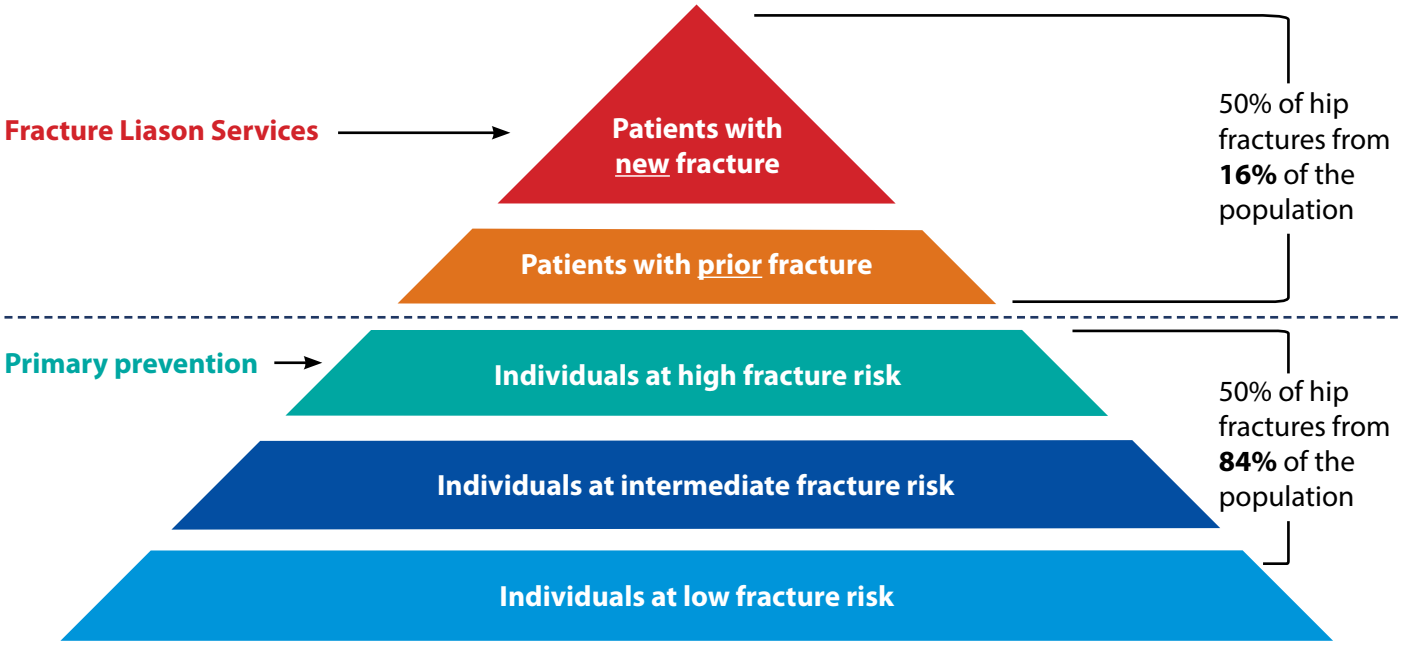
ESSENTIAL OSTEOPOROSIS MANAGEMENT FOR THE PRIMARY CARE PROVIDER

Introduction

Most individuals will experience deterioration in bone with advancing age, with consequent increases in fragility fractures. In addition, falls become more frequent with age, further increasing fracture risk. It is important to note that osteoporotic fractures impair quality of life and lead to increased dependency to a much greater degree in elderly individuals. Because of menopause-related declines in estrogen, women have greater bone loss and increases in fragility fracture compared to men. Our increased understanding of osteoporosis, its epidemiology, fracture risk, and expanding management options provide excellent opportunities for clinicians to benefit patients and maintain quality of life in aging individuals.

Osteoporosis Care Gap

Osteoporosis is a chronic disorder with great human costs as well as societal expense. There are many opportunities to intervene and benefit individuals at risk of fracture, both with primary prevention (prior to fragility fracture) and secondary prevention (subsequent to fragility fracture). This is analogous to managing patients at risk of myocardial infarction. Cholesterol, blood pressure, diabetes mellitus, and other risk factors are predictive of cardiovascular events, but most predictive is a prior myocardial infarction. In osteoporosis care, bone density and tools such as FRAX to estimate 10-year fracture risk can be helpful predictors, but are not nearly as potent as recognizing patients who have already had osteoporotic fragility fracture. These individuals are at the highest risk of future fracture events. By evaluating patients subsequent to acute osteoporotic fracture or with prior diagnosed osteoporotic fracture, one could screen only 16% of the postmenopausal female population to identify 50% of individuals who may proceed to hip fracture (**Figure 1**). These prevalent fracture patients, especially those having experienced a recent fragility fracture, can be easily identified since they have need of orthopedic, physiotherapy, cast clinic, rehabilitation medicine, and often in-patient care. Numerous cost economic models for identifying patients for secondary fracture prevention (after the initial osteoporotic fracture) have been published.[1] Fracture Liaison Services (FLS)



The majority of post-menopausal women (84%) have not suffered a fragility fracture. Strategies to case-find new and prior fracture patients could identify up to **50% of all potential hip fracture cases from 16% of the population.**

Figure 1. Fracture liaison services' role in identifying patients at high risk of fragility fracture.[14] Curr Med Res Opin 2005;21:4:475-482 Brankin E et al.; *courtesy of David Kendler, MD*

employ healthcare professionals to identify fragility fracture patients from facilities including the emergency room, cast clinics, and hospital wards and direct them to appropriate evaluation and osteoporosis management. Such FLS programs are present in many but not all care facilities.

Role of The Family Care Provider in Addressing The Osteoporosis Care Gap

Primary care providers can be instrumental in discussing osteoporosis and fracture risk with their patients. Frequently patients will attribute fractures to the force of their fall rather than bone strength. Obviously, all fractures are in part related to the force of the fall and in part related to the strength of the bone. Although not all fractures are fragility fractures, in individuals over age 65 the vast majority of fractures are related to bone strength and are amenable to osteoporosis therapies. Primary care providers can help counsel patients after fragility fracture by utilizing the three talking points for post-fracture patients identified by the American Society for Bone and Mineral Research (ASBMR) **(Table 1)**. Family doctors can screen their patients for fracture risk beginning around age 50. Those with clinical risk factors may be appropriate to proceed to bone density testing and 10-year fracture risk determination by FRAX. FRAX integrates clinical risk factors with BMD, providing greater acumen in identifying patients in need of osteoporosis pharmacotherapy and also helping primary care providers explain to their patients

• Their broken bone likely means they have osteoporosis and are at high risk for breaking additional bones, especially over the subsequent 1-2 years
• Breaking bones means they may, for example, have to use a walker, cane or wheelchair, or relocate from their home to a residential facility and will be at higher risk for dying prematurely
• Most importantly, there are actions they can take to reduce their risk

Table 1. Primary care communication to patients after hip or vertebral fracture: Three simple messages to patients and their family/caregivers throughout their fracture care.[15]; *courtesy of David Kendler, MD*

why treatment may or may not be required. If patients are identified, screening for the secondary cause of bone loss is important. In addition to clinical history and physical examination, chemistries may be helpful **(Table 2)**. Lateral thoracic and lumbar spine radiographs with instructions for the radiologist to identify vertebral fractures may be helpful with stratification of fracture risk. Family doctors may also provide specialist referrals for those patients at very high

risk, with treatment contraindications, or with complicated secondary osteoporosis etiologies.

Diet and Lifestyle Advise For Patients at Risk of Fracture

Dietary calcium sources may be deficient in elderly individuals, requiring dietary counselling or calcium supplementation. If an individual is able to achieve 3 or 4 dairy servings or the equivalent per day, a calcium supplement is not required. However, if dietary calcium is limited to 2 servings, a 500 mg calcium supplement taken with a meal will help to achieve the 1200 mg elemental calcium daily which is recommended. Vitamin D is synthesized in the skin after sunlight exposure, however older individuals have less effective synthesis of vitamin D, and there are few dietary sources of vitamin D. Although vitamin D stores can be assayed by serum 25 hydroxy vitamin D testing, this is expensive and not recommended for screening. A dosage of 1000 to 2000 IU vitamin D3 by daily supplement should achieve vitamin D sufficiency in the majority of elderly individuals. The Institute of Medicine tolerable upper limit of vitamin D supplementation is 4000 IU daily.[2] Many patients ask about other minerals and supplements. Although marketing messages are common, there is no evidence of the need for routine supplementation of magnesium, vitamin K2, boron, collagen, or complex calcium supplements. Patients should understand that magnesium is a laxative and may be helpful to relieve constipation, but if taken in excess may result in diarrhea. Especially for older patients with high fracture risk, and an exercise prescription is required. Exercise can offset muscle loss, weakness, frailty, and fall risk. There are many resources identifying interventions such as gait and balance training, to reduce the risk of fall https://osteoporosis.ca/exercise-recommendations/.[3]

Serum Chemistries: Calcium, Phosphate, Alkaline Phosphatase, Albumin, creatinine, eGFR, Complete blood count, 25-OH vitamin D, 24-hour urine calcium, Thyroid function tests (TSH, Free T4), Celiac antibodies, Serum/Urine Protein Electrophoresis.
Laboratory Tests in Specific Cases: Parathyroid hormone (PTH), Ionized Calcium, Total, Free, Bioavailable Testosterone, estradiol, LH, FSH, Prolactin, CTX (marker of bone resorption), Magnesium, Tryptase, urinary free cortisol.
X-rays of thoracic and lumbar spine
Screening tests for secondary causes of bone loss and bone fragility

Table 2. Blood chemistries for screening for the secondary cause of bone loss; *courtesy of David Kendler, MD*

Stratifying Patients By Degree of Fracture Risk: Very High Fracture Risk Patients

As a variety of osteoporosis therapies with varying actions and significantly different costs are available, the clinician must identify patients at very high fracture risk and target them to our most potent and rapidly-acting treatments. Patients at high risk of fracture may be effectively managed initially with less potent treatments. Patients with a recent osteoporotic fracture are at the highest risk of subsequent fracture and this risk is greatest in the first 1 to 2 years after their index fracture event. Data from Sweden, Iceland, USA, and Canada all support the concept of "imminent fracture risk" with very high fragility fracture risk early after index fracture.[4-7] Fragility fracture identifies patients at imminent risk for subsequent fracture. A recent update to FRAX, "FRAXplus®" allows integration of index fracture site and recency as well as other clinical risk factors not included in FRAX.[8] In order to aid the clinician in stratifying patients, recent guidelines, such as those published by the American Association of Clinical Endocrinologists (AACE) have proposed clinical criteria for very high fracture risk **(Figure 2, Table 3)**.[9]

Oral Antiresorptive Agents

Available oral antiresorbers include estrogen, selective estrogen receptor modulators (SERMs) (raloxifene, bazodoxifene), and oral bisphosphonates (alendronate, risedronate). Oral antiresorptive therapies preserve the existing bone architecture usually with transient modest increases in bone density plateauing after 2 or 3 years of therapy. Oral or transdermal estrogen may be an appropriate antiresorber for the short-term management of symptomatic early postmenopausal women. SERMs may provide reduction in breast cancer risk as well as reduction in vertebral fracture risk but may not provide adequate fracture protection in older individuals. Generic oral bisphosphonates are inexpensive and offer a unique opportunity for medication interruption after 3 to 5 years of treatment. The disadvantages of oral bisphosphonates include gastrointestinal intolerance, impaired absorption in many individuals, and demonstrated poor adherence to therapy in most real-world studies.

Parenteral Antiresorbers

Although a bisphosphonate, intravenous zoledronic acid infusion has greater potency and longer persistence of effect compared to oral bisphosphonate. Intravenous infusion assures absorption and adherence to treatment for at least the subsequent year. Longer drug holidays are therefore possible in many patients after intravenous zoledronic acid infusion. Acute phase reaction is a flu-like syndrome subsequent to intravenous zoledronic acid infusion, in about 10% of individuals, usually lasting a few days but which may be severe.

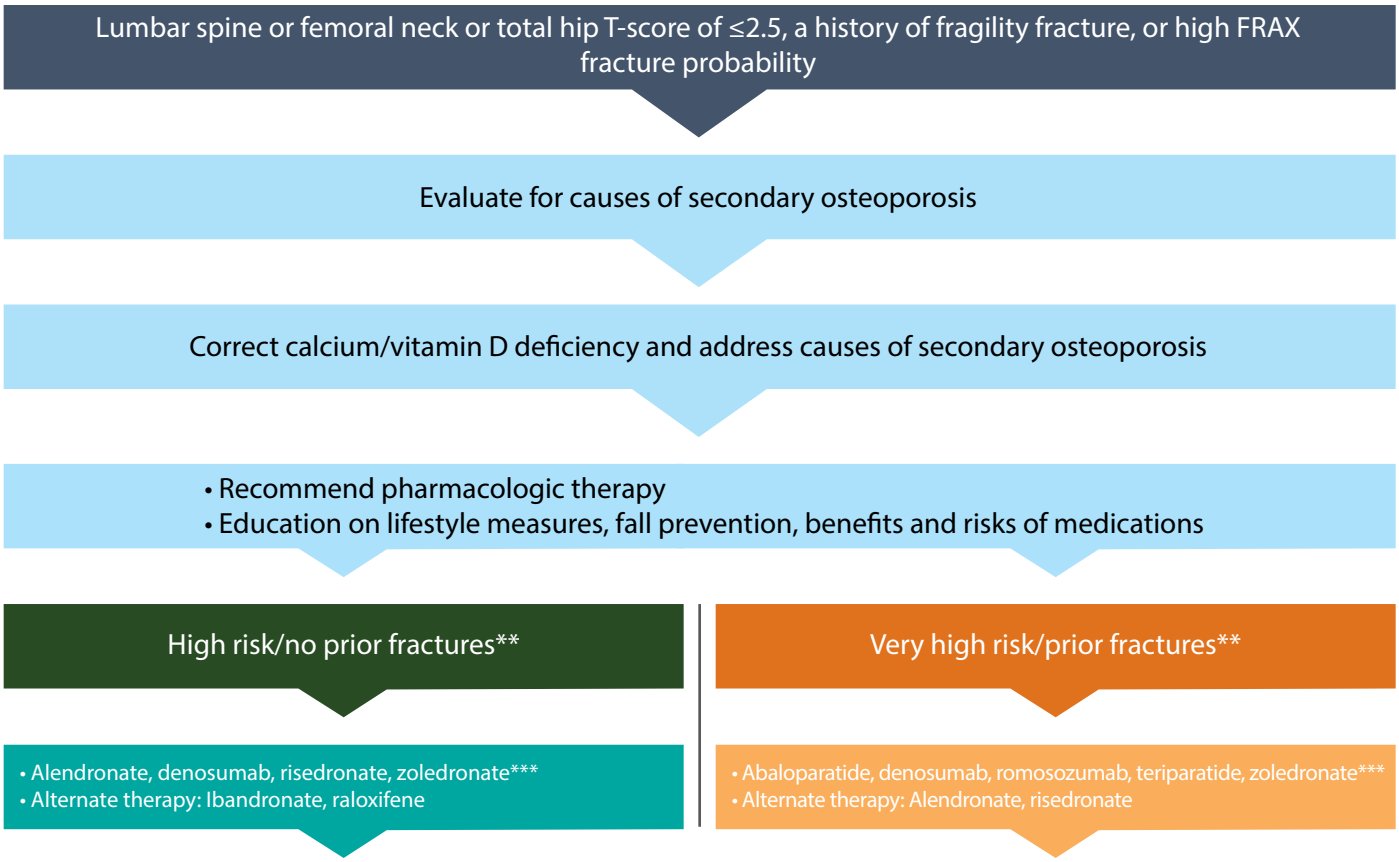


Figure 2. AACE clinical management algorithm for postmenopausal osteoporosis; *adapted from Camacho, PM et al., 2020*

Denosumab with six monthly subcutaneous injections provide RANK ligand monoclonal antibody, reducing number, function and survival of osteoclasts. This provides greater and ongoing improvements in BMD compared to bisphosphonates with greater anti-fracture efficacy. Like all other non-bisphosphonate treatments, if treatment is discontinued, antiresorptive effects reverse with consequent bone loss and the potential for fragility fractures in patients at risk. Therefore, patients discontinuing non-bisphosphonate antiresorptive therapy such as denosumab should be switched first to bisphosphonate, then after 3 to 5 years of bisphosphonate therapy, a subsequent bisphosphonate drug interruption may be possible.[10]

• Recent fracture (e.g., within the past 12 months)
• Fractures while on approved osteoporosis therapy
• Multiple fractures
• Fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids)
• Very low T-score (e.g., less than −3.0)
• High risk of falls or history of injurious falls
• Very high fracture probability by FRAX (e.g., major osteoporosis fracture >30%, hip fracture >4.5%)

Table 3. AACE criteria for determining very high fracture risk; adapted from Camacho, PM et al, 2020

Bone Anabolic Therapy

Bone anabolic therapy has a very different action on bone compared to antiresorptive therapy. With bone anabolic therapy, it is possible to reconstitute the trabecular and cortical bone architecture with much greater improvements in bone density, strength and demonstrated superior anti-fracture efficacy compared to antiresorbers. There are two different types of bone anabolic therapy: PTH receptor agonists therapies including teriparatide and abaloparatide both increase bone formation and bone resorption with the majority of new bone formation in the opened remodelling space. Romosozumab is a sclerostin monoclonal antibody with both antiresorptive and anabolic action on bone, forming most new bone on quiescent bone surfaces. Deciding between teriparatide and romosozumab is dependent in part on contraindications and in part on access and patient preference. Teriparatide requires daily

injections for two years at relatively high cost and with contraindication in patients with prior skeletal irradiation, Paget's disease, and skeletal malignancy. Romosozumab requires monthly injections for one year at relatively lower cost and with contraindication in patients with prior myocardial or cerebrovascular event.

Sequencing Osteoporosis Treatments/ Drug Holiday

A primary consideration regarding treatment sequence is that patients at very high fracture risk should be managed initially with bone anabolic therapy since initial antiresorptive therapy blunts subsequent bone anabolic therapy BMD response.[11] If a patient has inadequate response after oral antiresorptive therapy, they can progress to a parenteral antiresorber (zoledronic acid annual infusion, denosumab six monthly injections), or better still, to bone anabolic therapy (romosozumab or teriparatide). Although patients may express an interest in a "drug holiday," they should be made aware that this is available only to patients at low or moderate fracture risk after 3 to 5 years of bisphosphonate therapy. Clinicians are recommended to advise patients that bisphosphonates are like a persistent "coat of paint" on bone, therefore allowing moderate risk patients a two- or three-year bisphosphonate drug interruption with subsequent return to therapy.[12] It is important to explain that patients at high risk should not interrupt therapy (although they may switch to a parenteral antiresorber or bone anabolic therapy). Drug holiday is not recommended for other osteoporosis therapies including antiresorbers and bone anabolic therapy. Patients discontinuing non-bisphosphonate therapies should be switched to a bisphosphonate to prevent reversal of benefits to bone quality and anti-fracture efficacy.

Recent Osteoporosis Management Guidelines

A number of osteoporosis management guidelines have recently been developed by a variety of organizations representing physicians managing osteoporosis. Most guidelines do not have strict first- and second-line recommendations for therapy but rather, they encourage tailoring treatment to individual patient need. Although there are differences, most guidelines identify a "very high risk" population distinct from high-risk patients. This is helpful as it encourages physicians to stratify patients and direct the most potent and rapidly-acting agents to those at the highest risk of fracture. All guidelines encourage the recognition of prior fragility fracture as a prime risk factor for future fragility fracture. Most guidelines recognize that the lack of identification of fragility fracture patients is one of the leading causes of the osteoporosis care gap which must be addressed. All guidelines attempt to put in perspective the risks of osteonecrosis of the jaw and atypical fracture against the documented and substantial improvements in bone strength afforded by osteoporosis therapies.[13] Reevaluation of patients after 3 to 5 years of bisphosphonate therapy with potential drug holiday or switching to denosumab or anabolic therapy is recommended. Although there is no time limit to denosumab therapy, if discontinued, all guidelines recommend than an alternate antiresorber be initiated to prevent decline in BMD and return of fracture risk.

Conclusion

The past decade has seen significant advances in the understanding of osteoporosis epidemiology and fracture risk. In addition, we have new tools that are effective in reversing changes associated with menopause and maintaining normal bone turnover. Bone anabolic therapy should play a very important role in providing more effective fracture risk reduction for patients at very high fracture risk. Despite the advances made, there remains a significant care gap with many patients at high or very high fracture risk not being identified, not being evaluated, and not being afforded the opportunity to initiate treatment which would have significant benefits to their future independence and quality of life.

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References:

1. Danazumi MS, Lightbody N, Dermody G. Online effectiveness of fracture liaison service in reducing the risk of secondary fragility fractures in adults aged 50 and older: a systematic review and meta-analysis. *Osteoporos Int.* 2024 Mar 27.
2. Ross AC, Manson JE, Abrams SA, et al. The 2011 Report on dietary reference intakes for calcium and vitamin d from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab.* 2011 Jan; 96(1): 53-8.
3. https://osteoporosis.ca/exercise-recommendations/.
4. Adachi JD, Brown JP, Schemitsch E, et al. Fragility fracture identifies patients at imminent risk for subsequent fracture: real-world perspective database study in Ontario, Canada. *BMC Muscoloskelet Disord.* 2021 Feb 26;22(1):224.
5. Real-world retrospective database study in Ontario, Canada. *BMC Musculoskelet Disord.* 2021;22:224.
6. Balasubramanian A, Zhang J, Chen L, et al. Risk of subsequent fracture after prior fracture among older women. *Osteoporos Int.* 2019;30:79-92.
7. Johansson H, Siggeirsdottir K, Harvey NC, et al. Imminent risk of fracture after fracture. *Osteoporos Int.* 2017;28:775-80.
8. https://www.fraxplus.org/
9. Camacho PM. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis—2020 Update. *Endocrine Practice.* 2020 May;26(Suppl 1):1-46.
10. Kendler DL, Cosman F, Stad RK, et al. Denosumab in the treatment of osteoporosis: 10 years later: a narrative review. *Adv Ther.* 2022;39:58-74.
11. Cosman F, Kendler DL, Langdahl BL, et al. Romosozumab and antiresorptive treatment: the importance of treatment sequence. *Osteoporos Int.* 2022;33:1243-56.
12. Adler RA et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. *Journal of Bone and Mineral Research.* 2016;31(1):16–35.
13. Black DM, Geiger EJ, Eastell R, et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med.* 2020;383:743-53).
14. Brankin E, Mitchell C, Monroe R & on behalf of Lanarkshire Osteoporosis Service. *Curr Med Res Opin.* 2005;21:4:475-82.
15. https://www.asbmr.org/about/news-release-detail/press-release-asbmr-coalition-clinical-recommendat.