50 years of age will break a bone as a result of osteoporosis, resulting in $19 billion in related costs every 2 years and 2 million broken bones. With the aging population, these numbers are estimated to rise to 3 million fractures and $25.3 billion in costs annually by 2025.

- There are numerous randomized controlled trials (RCTs) assessing the efficacy of denosumab. However, only one trial studied the clinically meaningful endpoint of fracture prevention. All other efficacy trials used percent change in bone mineral density (BMD) as the primary endpoint. BMD is a surrogate marker and change in BMD is poorly correlated to fracture prevention. There is one placebo-controlled trial that established the efficacy of denosumab (Prolia) with regard to decreased fracture risk. Denosumab (Prolia) reduces the risk of vertebral, hip, and non-vertebral fractures in post-menopausal women with osteoporosis over 36 months when compared to placebo.

- Denosumab (Prolia) has not been proven in reliable clinical studies to be more effective than bisphosphonates for treatment of osteoporosis.

- There are trials comparing denosumab (Prolia) to oral alendronate and IV zoledronic acid for the treatment of osteoporosis in post-menopausal women. The primary endpoint of these trials is BMD changes at 12 months and 24 which is not as clinically relevant as fracture data. One small RCT demonstrated greater osteoporotic fracture reduction for denosumab compared to alendronate; however, future longitudinal studies with longer follow-up and larger sample sizes are needed to confirm the efficacy difference between denosumab and bisphosphonates.

- The FRAX® tool (www.shef.ac.uk/FRAX) was developed by the World Health Organization (WHO) to evaluate fracture risk of patients. It integrates clinical risk factors with BMD at the femoral neck. The FRAX® tool provides the 10-year probability of fracture. The output is a 10-year probability of hip fracture and a 10-year probability of major osteoporotic fracture (forearm, shoulder, or clinical vertebral fracture).

- Treatment should be considered if the 10-year risk is 3% or more for hip fracture or 20% or more for “major” osteoporosis-related fracture based on the US-adapted WHO algorithm (FRAX® tool).

- The American Association for Clinical Endocrinology guidelines (2020) define osteoporosis as a BMD T-score at or lower than -2.5. However, a non- or low-traumatic fracture (fragility fracture) is considered osteoporosis regardless of T-score. The AACE guidelines include the following recommendations:

    - The AACE recommend either bisphosphonates (IV or oral) or denosumab as initial treatment options for patients with high risk osteoporosis without prior fracture. Guidelines do not give preference to one antiresorptive therapy over another. Bisphosphonates decrease the breakdown of bone and have been shown to increase BMD and reduce the incidence of fractures in patients with osteoporosis. Contraindications to bisphosphonates include hypocalcemia and severe renal impairment. In addition, oral bisphosphonates are contraindicated in patients with the inability to stand or sit upright for at least 30 minutes and may not be an appropriate option in patients with underlying gastrointestinal issues. However, use of IV bisphosphonates is still appropriate in these situations.

    - There is evidence to support the superiority of certain antiresorptive agents (Prolia and IV zoledronate) and anabolic agents (Evenity®, Tymlos®, and Forteo®) over oral bisphosphonates for individuals who are unable to use oral bisphosphonates and as initial therapy for individuals with osteoporosis who are considered to be at very high risk for fracture, such as those with a T-score less than -3.0 or those with a history of fracture.

    - Sequential treatment with a bisphosphonate or denosumab (Prolia) is recommended after discontinuation of an anabolic agent to prevent bone density decline and loss of fracture efficacy.

- Until the effect of combination therapy on fracture risk is better understood, the AACE does not recommend concomitant use of FDA approved osteoporosis agents for the prevention or treatment of postmenopausal osteoporosis.

- The goal of monitoring osteoporosis therapy is to identify those who have significant bone loss. AACE recommends a repeat DXA scan 1 to 2 years after initiation of therapy until bone density is stable. Bone turnover markers (BTMs) are also useful for assessing patient compliance and efficacy of therapy. Reductions in BTMs are conferred by antiresorptive therapy and are associated with fracture reduction. Significant increases in BTMs indicate good response to anabolic therapy.

- A drug holiday is not recommended for denosumab (Prolia), and treatment with denosumab should be continued for as long as clinically appropriate. If denosumab therapy is discontinued, patients should be transitioned to another antiresorptive therapy.

- Glucocorticoid-Induced Osteoporosis:

  - A 24-month international, multi-center, double-blind, active controlled, double-dummy, non-inferiority study compared denosumab to risedronate. Of the 795 patients enrolled, 505 were glucocorticoid-continuing and 290 were initiating therapy. Denosumab was both non-inferior and superior to risedronate at 12 months for effect on BMD at the lumbar spine in both glucocorticoid-continuing (4.4% [95% CI 3.8–5.0] vs 2.3% [1.7–2.9]; p<0.0001) and glucocorticoid-initiating (3.8% [3.1–4.5] vs 0.8% [0.2–1.5]; p<0.0001) subpopulations. Incidence of adverse events, serious adverse events (including infections), and fractures was similar between treatment groups.

  - Guidelines from the American College of Rheumatology (ACR) for the prevention and treatment of glucocorticoid-induced osteoporosis (2017) include the following recommendations:

    - For adults with moderate- or high-risk of fracture, the ACR recommends treatment with an oral bisphosphonate over IV bisphosphonates, denosumab, teriparatide, or raloxifene.

    - Oral bisphosphonates are preferred as first-line treatment due to established safety and lower cost. Additionally, the ACR guidelines note that there is a lack of safety data for denosumab in patients treated with immunosuppressive agents.

- Prevention of Osteoporosis Due to Hormone Suppression:

  - In breast and prostate cancer patients on hormone suppression therapy, hormone suppression increases bone turnover and decreases bone mineral density (BMD). Oral bisphosphonates are the best value for the prevention of osteoporosis in patients on hormone suppression therapy.

  - There is a limited body of evidence for fracture prevention during hormone suppression therapy. Clinical trials were designed to demonstrate an increase in BMD without evidence of fracture prevention. BMD is a surrogate for fracture risk, the more clinically meaningful measure of efficacy.

  - For prevention of osteoporosis in patients with prostate cancer during androgen deprivation therapy (ADT): there is evidence that denosumab, pamidronate, zoledronic acid and alendronate increase BMD during ADT. NCCN Prostate Cancer guidelines (2022) recommend denosumab every 6 months, zoledronic acid once annually, or alendronate 70 mg once weekly when risk of fracture warrants treatment. Zoledronic acid increases BMD when administered every three months OR annually. There is no comparative evidence that demonstrates that more frequent dosing is more effective. One randomized, double-blind prospective study that compared denosumab compared to oral alendronate in 234 male patients undergoing ADT for prostate

cancer found that denosumab was associated with a lower rate of new vertebral fractures; however, additional randomized clinical studies are warranted to establish the superiority of denosumab in this clinical setting.

- There is evidence to support the use of antiresorptive agents (bisphosphonates and denosumab) to maintain or improve bone mineral density and reduce the risk of fractures in postmenopausal women who are receiving adjuvant aromatase inhibitor therapy. Unlike bisphosphonates, which have demonstrated an overall survival (OS) benefit when used as adjuvant therapy, there is no available data showing an OS benefit with denosumab. Therefore, the NCCN Breast Cancer guidelines (2023) recommend bisphosphonate therapy for postmenopausal patients receiving adjuvant endocrine therapy.

- Giant Cell Tumor of Bone (GCTB):

  - Several Phase II trials have examined the efficacy of denosumab for treating primary and recurrent giant cell tumor of the bone (GCTB). In an open-label, Phase II study (N = 37), denosumab induced tumor response (defined as elimination of at least 90% of giant cells or no radiologic progression of the target lesion for up to 25 weeks) in 86% of patients with unresectable or recurrent GCTB.

  - The NCCN Bone Cancer guidelines (2022) recommend denosumab and/or serial embolization as preferred options for patients with lesions that are resectable with unacceptable morbidity and/or unresectable axial lesions. Following primary treatment, patients with stable or improved disease can be observed. Intralesional excision is recommended if the lesion becomes resectable. Patients with unresectable disease should be re-treated with denosumab, serial embolization, and/or interferon-alfa-2b. Guidelines recommend continuation of treatment until disease progression.

- Cancer-Related Bone Metastases:

  - Zoledronic acid (Zometa) provides the best value for prevention of skeletal complications, decreasing the incidence and rate of skeletal events, and delaying skeletal events in women with breast cancer with bone metastases. The effectiveness of denosumab was evaluated in 7,201 patients with various advanced cancers including metastatic breast, prostate, and various other solid tumor cancers. There are four randomized controlled trials comparing denosumab (Xgeva) with zoledronic acid (Zometa) for the prevention of skeletal-related events related to bone metastases.

    - Skeletal-related events (SRE) related to bone metastases were defined as pathological fractures, spinal cord compression, and bone complications that required radiation or surgery.

    - The pooled result demonstrated that denosumab (Xgeva) was significantly superior to zoledronic acid (Zometa) in delaying the time to the first skeletal related event (HR: 0.86; 95% CI: 0.80-0.93; $p < 0.01$), and time to first-and-subsequent SREs (RR: 0.87; 95% CI: 0.81-0.93, $p < 0.01$). However, no significant differences were observed between the two groups in regard to overall survival (OS) or time to disease progression. Additionally, denosumab (Xgeva) was associated with higher incidence of hypocalcemia and osteonecrosis of the jaw (ONJ) compared to zoledronic acid (Zometa). Further analysis is warranted for the comparison of denosumab (Xgeva) and zoledronic acid (Zometa) for advanced cancer with bone metastasis.

  - Denosumab (Xgeva) extends the time to first SRE by six months in patients with metastatic breast cancer. As a secondary endpoint the number of SREs was reported (number of SREs is the more commonly reported endpoint in efficacy trials). In the metastatic breast cancer trial, 30.7% of denosumab (Xgeva) subjects had an SRE compared with 36.5% of zoledronic acid (Zometa) subjects. This small difference of 5.8%, coupled with the dropout rate of 18% could have influenced the magnitude of difference between the

products. It is unclear that that the treatment effect would be as robust if the subjects who left the trial early had completed the trial.

- The claim of superiority in other metastatic solid tumor cancers including prostate cancer is uncertain due to the small treatment effect and high drop-out rates. The drop-out rate (patients who did not complete the trial for reasons other than having an on-study SRE, death or disease progression) was greater than 22% in both trials. Therefore, it is uncertain that study groups remained adequately randomized and balanced by the end of the trials for a fair comparison.

- Prevention of Skeletal Related Events in patients with Multiple Myeloma (MM):

  - A randomized, double blind, active controlled, noninferiority trial compared denosumab and zoledronic acid. It enrolled 1,718 patients with newly diagnosed multiple myeloma (MM). The study met its primary endpoint. Denosumab was found to be non-inferior to zoledronic acid in delaying the time to first SRE following randomization, with a median time of 22.8 months for denosumab and 24 months for zoledronic acid (HR = 0.98, 95% CI, 0.85-1.14). An SRE was defined as a pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results for overall survival (OS) were comparable between Xgeva and zoledronic acid treatment groups with a hazard ratio of 0.90 (95% CI: 0.70, 1.16).

  - The NCCN Guidelines for Multiple Myeloma (2022) recommend bisphosphonates (category 1) or denosumab for all patients receiving therapy for symptomatic MM regardless of documented bone disease. With respect to duration of therapy, the guidelines recommend continuing bone-targeting treatment for up to 2 years and continuing beyond 2 years based on clinical judgement.

- Clinical Efficacy in hypercalcemia of Malignancy (HCM):

  - HCM is a serious complication that is indicative of poor malignancy prognosis. It results from cancer-driven increases in bone resorption, and if untreated, can lead to renal failure, progressive mental impairment, coma, and death.

  - The classification of severity of hypercalcemia is as follows:

    - Mild hypercalcemia: albumin CSC <12 mg/dL

    - Moderate hypercalcemia: albumin CSC between 12 and 14 mg/dL

    - Severe hypercalcemia: albumin CSC >14 mg/dL

  - Denosumab (Xgeva) acts by inhibiting the osteoclast-mediated bone resorption, which results in decrease in bone destruction and calcium release thus lowering calcium levels in HCM patients.

  - An open-label, single-arm study evaluated 33 patients with advanced cancer and persistent hypercalcemia (CSC of 12.5mg/dL or higher) after recent bisphosphonate treatment. The primary endpoint was the proportion of patients with a response (defined as albumin-corrected serum calcium (CSC) <11.5 mg/dL within 10 days after the first dose of Xgeva)

  - The secondary endpoints included the proportion of patients who experienced a complete response (defined as CSC <10.8 mg/dL by day 10), time to response, and response duration (defined as the number of days from the first occurrence of CSC <11.5 mg/dL)

- Please refer to study results in Table 1 below:

Table 1: Efficacy of Xgeva in Patient with HCM Refractory to Bisphosphonate Therapy

Endpoint	N = 33	Proportion (%)
All Responders (CSC≤ 11.5 mg/dL) by day 10	21	63.6
All Responders by Day 57	23	69.7
Complete Responders (CSC≤ 10.8 mg/dL) by day 10	12	36.4
All Complete Responders by Day 57	21	63.6

References:

1. Prolia [prescribing information]. Amgen, Inc. May 2022.
2. Xgeva [prescribing information]. Amgen, Inc. June 2020.
3. Forteo [prescribing information]. Indianapolis, IN: Eli Lilly; September 2021.
4. Tymlos [prescribing information]. Morristown, NJ: Alvogen; December 2022.
5. Evenity [prescribing information]. Waltham, MA: Radius Health; April 2020.
6. Bisphosphonates. Facts and Comparisons. 2022. Available from Wolters Kluwer Health, Inc.
7. FDA Approves Xgeva (denosumab) for Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy. http://www.drugs.com/newdrugs/fda-approves-xgeva-denosumab-hypercalcemia-malignancy-refractory-bisphosphonate-therapy-4117.html. Accessed Jan 16, 2015.
8. 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. doi:10.4158/GL-2020-0524SUPPL
9. Lyu H, Jundi B, Xu C, et al. Comparison of Denosumab and Bisphosphonates in Patients With Osteoporosis: A Meta-Analysis of Randomized Controlled Trials. J Clin Endocrinol Metab. 2019;104(5):1753-1765. doi:10.1210/jc.2018-02236
10. Nakamura T, Matsumoto T, Sugimoto T, et al. Clinical Trials Express: fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: denosumab fracture intervention randomized placebo controlled trial (DIRECT). J Clin Endocrinol Metab. 2014;99(7):2599-2607. doi:10.1210/jc.2013-4175
11. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis [published correction appears in Arthritis Rheumatol. 2017 Nov;69(11):2246]. Arthritis Rheumatol. 2017;69(8):1521-1537. doi:10.1002/art.40137
12. Saag KG, Pannacciulli N, Geusens P, et al. Denosumab Versus Risedronate in Glucocorticoid-Induced Osteoporosis: Final Results of a Twenty-Four-Month Randomized, Double-Blind, Double-Dummy Trial. Arthritis Rheumatol. 2019;71(7):1174-1184. doi:10.1002/art.40874
13. NCCN Guidelines Version 2.2023. Bone Cancer. Published September 28, 2022.
14. NCCN Guidelines Version 1.2023. Prostate Cancer. Published September 16, 2022.
15. Doria C, Mosele GR, Solla F, Maestretti G, Balsano M, Scarpa RM. Treatment of osteoporosis secondary to hypogonadism in prostate cancer patients: a prospective randomized multicenter international study with denosumab vs. alendronate. Minerva Urol Nefrol. 2017;69(3):271-277. doi:10.23736/S0393-2249.16.02808-3
16. NCCN Guidelines Version 2.2023. Breast Cancer. Published February 7, 2023.
17. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol. 2018;19(3):370-381. doi:10.1016/S1470-2045(18)30072-X
18. Jiang L, Cui X, Ma H, Tang X. Comparison of denosumab and zoledronic acid for the treatment of solid tumors and

multiple myeloma with bone metastasis: a systematic review and meta-analysis based on randomized controlled trials. J Orthop Surg Res. 2021;16(1):400. Published 2021 Jun 22. doi:10.1186/s13018-021-02554-8
19. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28(35):5132-5139. doi:10.1200/JCO.2010.29.7101
20. NCCN Guidelines Version 3.2023. Multiple Myeloma. Published December 8, 2022.
21. Chakhtoura M, El-Hajj Fuleihan G. Treatment of Hypercalcemia of Malignancy. Endocrinol Metab Clin North Am. 2021;50(4):781-792. doi:10.1016/j.ecl.2021.08.002
22. Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcemia of malignancy. J Clin Endocrinol Metab. 2014;99(9):3144-3152. doi:10.1210/jc.2014-1001

Policy/UM Medical Management System Update History		
#	Date	Change Description
1.3	Effective Date: 04/06/2023	Updated policy to clarify duration of initial authorization period for Prolia and Xgeva
1.2	Effective Date: 10/06/2022	Shortened duration of bisphosphonate trial to 12 months for osteoporosis indication for Prolia; removed requirement for calcium/vitamin D supplementation for all indications; will not allow for combination therapy with bisphosphonates in addition to anabolic therapies
1.1	Effective Date: 10/07/2021	Annual Review of Medical Policy
1.0	Effective Date: 10/08/2020	Medical policy established

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*