



MEDICAL COVERAGE POLICY

SERVICE: Bone Turnover Markers for the Diagnosis and Management of Osteoporosis and Other Conditions Associated with Increased Bone Turnover

Policy Number: 029

Effective Date: 04/01/2024

Last Review: 03/11/2024

Next Review: 03/11/2025

Important note: Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.

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PRIOR AUTHORIZATION: Not applicable. Not required for Medicare lines of business.

POLICY: Please review the plan’s EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

[NCD 190.19 Collagen Crosslinks, any Method](#)

“Indications: Generally speaking, collagen crosslink testing is useful mostly in “fast losers” of bone. The age when these bone markers can help direct therapy is often pre-Medicare. By the time a fast loser of bone reaches age 65, she will most likely have been stabilized by appropriate therapy or have lost so much bone mass that further testing is useless. Coverage for bone marker assays may be established, however, for younger Medicare beneficiaries and for those men and women who might become fast losers because of some other therapy such as glucocorticoids. Safeguards should be incorporated to prevent excessive use of tests in patients for whom they have no clinical relevance. Collagen crosslinks testing is used to:

1. Identify individuals with elevated bone resorption, who have osteoporosis in whom response to treatment is being monitored.
2. Predict response (as assessed by bone mass measurements) to FDA approved antiresorptive therapy in postmenopausal women.
3. Assess response to treatment of patients with osteoporosis, Paget’s disease of the bone, or risk for osteoporosis where treatment may include FDA approved antiresorptive agents, anti-estrogens or selective estrogen receptor moderators”

Limitations and Frequency: “Because of significant specimen to specimen collagen crosslink physiologic variability (15-20%), current recommendations for appropriate utilization include: one or two base-line



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assays from specified urine collections on separate days; followed by a repeat assay about 3 months after starting anti-resorptive therapy; followed by a repeat assay in 12 months after the 3-month assay; and thereafter not more than annually, unless there is a change in therapy in which circumstance an additional test may be indicated 3 months after the initiation of new therapy.”

For Medicaid plans, please confirm coverage as outlined in the [Texas Medicaid Provider Procedures Manual | TMHP](#) (TMPPM). If there are no applicable criteria to guide medical necessity decision making in the TMPPM, use the criteria set forth below.

BSWHP considers the use of non-evidence-based bone turnover markers for the diagnosis and management of osteoporosis and other conditions associated with increased bone turnover to be experimental and investigational and not medically necessary.

BACKGROUND:

After cessation of growth, bone is in a constant state of remodeling, (or turnover).

Two basic types of biochemical markers can assess bone turnover:

- Markers of bone resorption, and
- Markers of bone formation.

Additionally, they can be categorized into two groups:

- Markers that measure substances released by osteoblasts and osteoclasts, and
- Markers that measure substances produced during the formation or breakdown of a collagen, a protein found in bone.

Commercially available tests are available to assess some of these markers in urine and/or serum by High Performance Liquid Chromatography (HPLC) or immunoassay. Assessment of bone turnover markers is proposed to supplement bone mineral density (BMD) measurement in the diagnosis of osteoporosis, and aid in treatment decisions. Bone turnover markers could also potentially be used to evaluate treatment effectiveness before changes in BMD can be observed.

Bone turnover is correlated with the presence of certain biochemical markers in serum and/or urine that result from net activity in bone throughout the entire skeleton. In contrast, bone mass measurements (e.g., bone density studies) and radiographs (e.g., x-rays) provide a static picture of a specific skeletal site.

Collagen cross links are generally reliable markers of bone resorption because they are stable in serum



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and urine. These markers links bind three molecules of collagen in the bone and are released from the bone matrix after resorption, either free or bound to the N- or C- telopeptide of collagen. Collagen cross links may be detected using either high-pressure liquid chromatography (HPLC)-fluorometric assays (Pyr, D-Pyr), or immunoassays (Pyr, D-Pyr, CTx, NTx). In addition to collagen cross links, ALP is a commonly used marker due to its ease of measurement; however, it lacks sensitivity and specificity for detecting osteoporosis since only about half of the ALP activity is derived from bone. Bone-specific alkaline phosphatase (B-ALP) is a better marker of bone formation than ALP. Serum osteocalcin is a small noncollagenous protein that is a product of osteoblasts and thus increased levels reflect bone formation. Tartrate-resistant acid phosphatase (TRAP) is produced by osteoclasts; it is thought to be active in bone matrix degradation.

The literature suggests that alternative measures of bone strength have the potential to assess individual responses to treatment or identify individuals at high risk of future fracture, thereby potentially altering clinical management. However, there is insufficient evidence that current methods for measuring bone turnover markers are sufficiently sensitive to reliably determine individual treatment responses. Measurement of bone turnover has not been shown to improve health outcomes.

MANDATES: None

CODES:

Important note: Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.

CPT Codes	82523 Collagen cross links, any method (Medicare lines of business ONLY)
CPT Codes NOT covered:	82523 Collagen cross links, any method 82607 Cyanocobalamin (Vitamin B-12) 82608 Cyanocobalamin (Vitamin B-12); unsaturated binding capacity 83090 Homocysteine 83937 Osteocalcin (bone g1a protein)



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ICD-10 codes	<p>M80.00X+ - M81.8 - Age-related osteoporosis with or without current Pathological fracture</p> <p>N25.0 - Renal osteodystrophy [for persons receiving serotonergic anti-depressants]</p> <p>Q78.0 - Osteogenesis imperfecta</p> <p>Z13.820 - Encounter for screening for osteoporosis</p>
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POLICY HISTORY:

Status	Date	Action
New	1/6/2010	New policy
Reviewed	12/6/2011	Reviewed.
Reviewed	10/25/2012	Reviewed.
Reviewed	10/3/2013	Minor changes. Added NCD from 2003 190.19 for reference
Reviewed	07/24/2014	No changes
Reviewed	08/11/2015	No changes
Reviewed	08/18/2016	No changes
Reviewed	08/08/2017	No significant changes
Reviewed	05/29/2018	No significant changes
Reviewed	08/22/2019	No significant changes. Added ICD-10 codes
Reviewed	09/22/2020	Re-formatted for SWHP / FirstCare
Reviewed	09/23/2021	No changes
Reviewed	09/22/2022	No changes
Reviewed	11/29/2023	Formatting changes, added hyperlinks to NCD and TMPPM, beginning and ending note sections updated to align with CMS requirements and business entity changes
Reviewed	03/11/2024	Corrected the "For Medicaid Plans" section to utilize this Medical Policy if TMPPM does not have medical necessity guidance.

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.



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1. Salamone, L.M., Pressman, A.R., et al. Estrogen replacement therapy. A survey of older women's attitudes. Archives of Internal Medicine (1996) 156(12):1293-7.
2. Garnero, P., Hausherr, E., et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. Journal of Bone and Mineral Research (1996) 11(10):1531-8.
3. Arnaud, C.D. Osteoporosis: using 'bone markers' for diagnosis and monitoring. Geriatrics (1996 April) 51(4):24-30.
4. Withold, W. Monitoring of bone turnover biological, preanalytical and technical criteria in the assessment of biochemical markers. European Journal of Clinical Chemistry and Clinical Biochemistry (1996 October) 34(10):785-99
5. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis and Rheumatism (1996); 39(11):1791-801.
6. Bone, H.G., Downs, R.W., et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Journal of Clinical Endocrine Metabolism (1997) 82(1):265-74
7. Bauer, D.C., Black, D.M., et al. Biochemical markers predict spine but not hip BMD response to bisphosphonates: the Fracture Intervention Trial (FIT). Journal of Bone and Mineral Research (1997) 12(suppl 1):S150.
8. Marcus, R., Holloway, L., et al. Turnover markers only weakly predict bone response to estrogen: the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI). Journal of Bone and Mineral Research (1997) 12(suppl 1):S103.
9. Eastell, R., and A. Blumshon. The value of biochemical markers of bone turnover in osteoporosis. Journal of Rheumatology (1997 June) 24(6):1215-7.
10. Melton, L.J. 3rd, et al. Relationship of bone turnover to bone density and fractures. Journal of Bone and Mineral Research (1997 July) 12(7):1083-91.
11. Blumsohn, A., and R. Eastell. The performance and utility of biochemical markers of bone turnover: do we know enough to use them in clinical practice? Annals of Clinical Biochemistry (1997 September) 34(Part 5):449-59.
12. Tanaka, Y., Funahashi, H., et al. Parathyroid function and bone metabolic markers in primary and secondary hyperparathyroidism. Seminars in Surgical Oncology (1997); 13(2):125-33.
13. Garnero, P., and P.D. Delmas. Biochemical markers for bone turnover. Applications for osteoporosis. Endocrinology and Metabolism Clinics of North America (1998 June) 27(2) 303- 23.
14. Rosalki, S.B. Biochemical markers of bone turnover. International Journal of Clinical Practitioners (1998 June) 52(4):2556.
15. Rosen C.J., and A. Tenenhouse. Biochemical markers of bone turnover. A look at laboratory tests that reflect bone status. Postgraduate Medicine (1998 October) 104(4):101-2, 107-10, 113-4.
16. Broyles, D.L., et al. Analytical and clinical performance characteristics of Tandem-MP Ostase, a new immunoassay for serum bone alkaline phosphatase. Clinical Chemistry (1998 October) 44(10): 2139-47
17. Recommended Medicare National Coverage Policy for Collagen Crosslinks, any method. Medicare (1998 November 11): 1-6 <http://cms.hhs.gov>.
18. Miller, P.D., Bonnick, S.L., et al. The challenges of peripheral bone density testing: which patients need additional central density skeletal measurements? Journal of Clinical Densitometry (1998) 1(3):211-8.
19. National Osteoporosis Foundation. Physician's Guide to Diagnosis and Management of Osteoporosis. Bell Meade, NJ: Excerpta Medica. 1998.
20. de Vernejoul, M.C. Markers of bone remodeling in metabolic bone disease. Drugs Aging (1998); 12(suppl 1):9-14.
21. Lindsay, R. Clinical utility of biochemical markers. Osteoporosis International (1999) 9(suppl 2):S29-32.
22. Miller, P.D., Zapalowski, C., et al. Bone densitometry: the best way to detect osteoporosis and to monitor therapy. Journal of Clinical Endocrinology and Metabolism (1999) 84(6):1867-71.
23. Miller, P.D., Baran, D.T., et al. Practical clinical application of biochemical markers of bone turnover. Consensus of an expert panel. Journal of Clinical Densitometry (1999) 2(3):323-42.



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24. Biochemical Markers of Bone Turnover. Merck Osteoporosis Education System - 1995-2000 Merck & Co., Inc. (2000) <http://www.merck.com>.
25. Looker, A.C., Bauer, D.C., et al. Clinical use of biochemical markers of bone remodeling: current status and future directions. *Osteoporosis International* (2000) 11(6):467-80.
26. Coble, Y.D., Abrams, S.A., et al. Managing Osteoporosis, Part 1: Detection and Clinical Issues in Testing. American Medical Association Continuing Education Program for Primary Care Physicians. American Medical Association. (2000 August) <http://www.ama-assn.org> (Accessed 3/13/2006).
27. Petak, S.M., Abrams, S.A., et al. Managing Osteoporosis, Part 4: Update in Patient Management. American Medical Association Continuing Education Program for Primary Care Physicians. American Medical Association. (2001 August) <http://www.ama-assn.org>
28. American Association of Clinical Endocrinologists. AACE Medical Guidelines for the Clinical Practice for the Prevention and Treatment of Postmenopausal Osteoporosis: 2001 Edition, with Selected Updates for 2003. Available at www.aace.com (accessed – 2006 March 13).
29. Black, D.M., Greenspan, S.L., et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *New England Journal of Medicine* (2003) 349(13):1207-15.
30. CMS National Coverage Determinations. Collagen Crosslinks, Any Method. (2003 January) www.cms.hhs.gov (accessed – 2006 February 16).
31. Hodgson, S.F., Watts, N.B., et al. American association of clinical endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 Edition, with selected updates for 2003. (2003 December) *Endocrine Practice* 9(6):544-564. <http://www.aace.com> (Accessed 3/14/2006).
32. Sambrook, P.N., Geusens, P., et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) *International Journal of Internal Medicine* (2004) 255(4):50311.
33. Meunier, P.J., Roux, C., et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *New England Journal of Medicine* (2004) 350(5):459-68.
34. Collagen Cross Links as Markers of Bone Turnover. Chicago, Illinois: Blue Cross Blue Shield Association Medical Policy Reference Manual (2004 December) Medicine 2.04.15
35. Sambrook, P.N., Geusens, P., et al. Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial). *International Journal of Internal Medicine* (2004); 255(4):50311.
36. Meunier, P.J., Roux, C., et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *The New England Journal of Medicine* (2004); 350(5):459-68.
37. Physician's guide for osteoporosis. National Osteoporosis Foundation. <http://www.nof.org> (Accessed 3/1/2006).
38. Välimäki, M.J., Farrerons-Minguella, J., et al. Effects of Risedronate 5 mg/d on bone mineral density and bone turnover markers in late-postmenopausal women with osteopenia: a multinational, 24-month, randomized, double-blind, placebo-controlled, parallel-group, phase III trial. *Clinical Therapeutics* (2007); 29(9):1937
39. Abe, Y., Ishikawa, H., et al. Higher efficacy of urinary bone resorption marker measurements in assessing response to treatment for osteoporosis in postmenopausal women. *The Tohoku Journal of Experimental Medicine* (2008); 214(1):519.
40. Shiraki, M., Kuroda, T., et al. Nonenzymatic collagen cross-links induced by glycooxidation (pentosidine) predicts vertebral fractures. *Journal of Bone and Mineral Metabolism* (2008); 26(1):93-100.
41. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Available at <http://www.nof.org> (accessed - 2008 August 4).
42. Abe, Y., Ishikawa, H., et al. Higher efficacy of urinary bone resorption marker measurements in assessing response to



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treatment for osteoporosis in postmenopausal women. The Tohoku Journal of Experimental Medicine (2008); 214(1):519.

- 43. Bergmann P, Body JJ, Boonen S et al. Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. Int J Clin Pract 2008; 63(1):19-26.
- 44. Shiraki M, Itabashi A. Short-term menatetrenone therapy increases gamma-carboxylation of osteocalcin with a moderate increase of bone turnover in postmenopausal osteoporosis: a randomized prospective study. J Bone Miner Metab 2009; 27(3):333-40.
- 45. Clinician's Guide to prevention and treatment of Osteoporosis. National Osteoporosis Foundation. <http://www.nof.org> (Accessed 10/28/2009).
- 46. CMS National Coverage Determinations. 190.19 Collagen Crosslinks, Any [Method](#). www.cms.hhs.gov (Accessed 10/28/2009).

Note:

Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid plans are offered through Scott and White Health Plan in the Central Managed Care Service Area (MRSA) and STAR and CHIP plans are offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSA's.