



Medical Policy

Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated with High Bone Turnover

Table of Contents

- [Policy: Commercial](#)
- [Description](#)
- [Information Pertaining to All Policies](#)
- [Authorization Information](#)
- [Policy History](#)
- [Coding Information](#)
- [References](#)

Policy Number: 549

BCBSA Reference Number: 2.04.15 (For Plan internal use only)

Related Policies

- Bone Mineral Density Studies, #[450](#)
- Vertebral Fracture Assessment with Densitometry, #[449](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Measurement of bone turnover markers is considered **INVESTIGATIONAL** to determine fracture risk in individuals with osteoporosis or with age-related risk factors for osteoporosis.

Measurement of bone turnover markers is considered **INVESTIGATIONAL** in the management of individuals with conditions associated with high rates of bone turnover, including but not limited to Paget's disease, primary hyperparathyroidism and renal osteodystrophy.

Measurement of bone turnover markers is considered **INVESTIGATIONAL** to determine response to therapy in individuals who are being treated for osteoporosis.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

CPT codes:	Code Description
82523	Collagen cross-links, any method

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
83937	Osteocalcin (bone g1a protein)

Description

Bone Turnover

After cessation of growth, bone is in a constant state of remodeling (or turnover), with initial absorption of bone by osteoclasts followed by deposition of new bone matrix by osteoblasts.¹ This constant bone turnover is critical to the overall health of the bone, by repairing microfractures and remodeling the bony architecture in response to stress. Normally, the action of osteoclasts and osteoblasts is balanced, but bone loss occurs if the 2 processes become uncoupled. Bone turnover markers can be categorized as bone formation markers or bone resorption markers and can be identified in serum and/or urine.² There is interest in the use of bone turnover markers to evaluate age-related osteoporosis, a condition characterized by slow, prolonged bone loss, resulting in an increased risk of fractures at the hip, spine, or wrist. Measurement of bone turnover markers may aid in the diagnosis (by determining fracture risk) and therapeutic monitoring (by determining response to treatment) of osteoporosis. Bone turnover markers may also be used for the management of other diseases associated with high bone turnover (eg, primary hyperparathyroidism, Paget disease, renal osteodystrophy). Table 1 summarizes the various bone turnover markers.³

Table 1. Bone Turnover Markers

Formation Markers	Resorption Markers
Serum osteocalcin	Serum and urinary hydroxyproline
Serum total alkaline phosphatase	Urinary total pyridinoline
Serum bone-specific alkaline phosphatase	Urinary total deoxypyridinoline
Serum procollagen I carboxyterminal propeptide	Urinary-free pyridinoline (also known as Pylilinks)
Serum procollagen type 1 N-terminal propeptide	Urinary-free deoxypyridinoline (also known as Pylilinks-D)
Bone sialoprotein	Serum and urinary collagen type I cross-linked N-telopeptide (also referred to as Osteomark)

	Serum and urinary collagen type I cross-linked C-telopeptide (also referred to as CrossLaps)
	Serum carboxy-terminal telopeptide of type I collagen
	Tartrate-resistant acid phosphatase

Summary

Description

Bone turnover markers are biochemical markers of either bone formation or bone resorption. Commercially available tests are available to assess some of these markers in urine and/or serum by high-performance liquid chromatography or immunoassay. Assessment of bone turnover markers is proposed to supplement bone mineral density measurement in the diagnosis of osteoporosis and to aid in treatment decisions. Bone turnover markers could also potentially be used to evaluate treatment effectiveness before changes in bone mineral density can be observed.

Summary of Evidence

For individuals with osteoporosis or risk factors for age-related osteoporosis who receive a measurement of bone turnover markers to determine fracture risk, the evidence includes observational studies on the association between markers and osteoporosis and fracture risk, and systematic reviews of those studies. Relevant outcomes are test validity and morbid events. Few studies have directly addressed whether any bone turnover markers beyond bone mineral density (BMD) measurements are independent predictors of fracture risk. One meta-analysis investigated the independent role of bone turnover markers in fracture risk prediction and found a statistically significant but modest association between bone turnover markers (specifically, PINP and CTX) and future fracture risk after adjusting for BMD and clinical risk factors. Other studies have suggested that bone turnover marker levels may be independently associated with osteoporosis and fracture risk in some groups, but there is insufficient evidence reporting on an association with any specific marker. Questions remain whether bone turnover markers are sufficiently sensitive to determine reliably individual treatment responses. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are being treated for osteoporosis who receive a measurement of bone turnover markers to determine response to therapy, the evidence includes an observational studies, randomized controlled trials (RCTs), and a systematic review of these RCTs. Relevant outcomes are test validity and morbid events. There is limited evidence on the impact of bone turnover markers on the management of osteoporosis. Individual RCTs and a systematic review of these RCTs have not found that feedback on bone turnover marker improves treatment adherence rates. No studies were identified that evaluated whether the use of bone turnover markers leads to management changes that are expected to improve outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with conditions associated with high rates of bone turnover other than age-related osteoporosis (eg, primary hyperparathyroidism, Paget disease, renal osteodystrophy) who receive a measurement of bone turnover markers, the evidence includes observational studies on the association between markers and disease activity and a systematic review of those studies. Relevant outcomes are test validity and morbid events. The largest amount of evidence has been published on Paget disease; a systematic review found correlations between several bone turnover markers and disease activity prior to and/or after bisphosphonate treatment. There is a lack of evidence on how the measurement of bone turnover markers can change patient management or improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy History

Date	Action
3/2025	Annual policy review. References updated. Policy statements unchanged.
3/2024	Annual policy review. Description, summary, and references updated. Policy statements unchanged.

3/2023	Annual policy review. Minor editorial refinements to policy statements; intent unchanged.
2/2022	Annual policy review. Policy statements unchanged.
3/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
6/2020	Annual policy review. New investigational indications described. Effective 6/1/2020.
2/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
3/2018	Annual policy review. New references added.
11/2015	Annual policy review. New references added.
7/2015	Clarified coding information.
6/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
1/2014	Annual policy review. New references added.
11/2013	Added ICD-9 diagnosis code 256.9 to be in alignment with the NCD.
10/2013	Added ICD-9 diagnosis codes 252.00-252.02, 252.08 to be in alignment with the NCD.
6/2013	Annual policy review. New investigational indications described. Effective 6/1/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
1/1/2011	New policy effective 1/1/2011 describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

References

1. Kim JM, Lin C, Stavre Z, et al. Osteoblast-Osteoclast Communication and Bone Homeostasis. Cells. Sep 10 2020; 9(9). PMID 32927921
2. Greenblatt MB, Tsai JN, Wein MN. Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease. Clin Chem. Feb 2017; 63(2): 464-474. PMID 27940448
3. Shetty S, Kapoor N, Bondu JD, et al. Bone turnover markers: Emerging tool in the management of osteoporosis. Indian J Endocrinol Metab. 2016; 20(6): 846-852. PMID 27867890
4. Szulc P, Naylor K, Hoyle NR, et al. Use of CTX-I and PINP as bone turnover markers: National Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. Osteoporos Int. Sep 2017; 28(9): 2541-2556. PMID 28631236
5. Tian A, Ma J, Feng K, et al. Reference markers of bone turnover for prediction of fracture: a meta-analysis. J Orthop Surg Res. Feb 28 2019; 14(1): 68. PMID 30819222
6. Johansson H, Odén A, Kanis JA, et al. A meta-analysis of reference markers of bone turnover for prediction of fracture. Calcif Tissue Int. May 2014; 94(5): 560-7. PMID 24590144
7. Biver E, Chopin F, Coiffier G, et al. Bone turnover markers for osteoporotic status assessment? A systematic review of their diagnosis value at baseline in osteoporosis. Joint Bone Spine. Jan 2012; 79(1): 20-5. PMID 21724445
8. Tamaki J, Iki M, Kadowaki E, et al. Biochemical markers for bone turnover predict risk of vertebral fractures in postmenopausal women over 10 years: the Japanese Population-based Osteoporosis (JPOS) Cohort Study. Osteoporos Int. Mar 2013; 24(3): 887-97. PMID 22885773
9. Bauer DC, Garnero P, Harrison SL, et al. Biochemical markers of bone turnover, hip bone loss, and fracture in older men: the MrOS study. J Bone Miner Res. Dec 2009; 24(12): 2032-8. PMID 19453262

10. Zhang T, Liu P, Zhang Y, et al. Combining information from multiple bone turnover markers as diagnostic indices for osteoporosis using support vector machines. *Biomarkers*. Mar 2019; 24(2): 120-126. PMID 30442069
11. Gutierrez-Buey G, Restituto P, Botella S, et al. Trabecular bone score and bone remodelling markers identify perimenopausal women at high risk of bone loss. *Clin Endocrinol (Oxf)*. Sep 2019; 91(3): 391-399. PMID 31141196
12. Shieh A, Greendale GA, Cauley JA, et al. Urinary N-Telopeptide as Predictor of Onset of Menopause-Related Bone Loss in Pre- and Perimenopausal Women. *JBMR Plus*. Apr 2019; 3(4): e10116. PMID 31044185
13. Bauer DC, Garnero P, Hochberg MC, et al. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. *J Bone Miner Res*. Feb 2006; 21(2): 292-9. PMID 16418785
14. Kashii M, Kamatani T, Nagayama Y, et al. Baseline serum PINP level is associated with the increase in hip bone mineral density seen with Romosozumab treatment in previously untreated women with osteoporosis. *Osteoporos Int*. Mar 2023; 34(3): 563-572. PMID 36585509
15. Baxter I, Rogers A, Eastell R, et al. Evaluation of urinary N-telopeptide of type I collagen measurements in the management of osteoporosis in clinical practice. *Osteoporos Int*. Mar 2013; 24(3): 941-7. PMID 22872068
16. Burch J, Rice S, Yang H, et al. Systematic review of the use of bone turnover markers for monitoring the response to osteoporosis treatment: the secondary prevention of fractures, and primary prevention of fractures in high-risk groups. *Health Technol Assess*. Feb 2014; 18(11): 1-180. PMID 24534414
17. Roux C, Giraudeau B, Rouanet S, et al. Monitoring of bone turnover markers does not improve persistence with ibandronate treatment. *Joint Bone Spine*. Jul 2012; 79(4): 389-92. PMID 21703900
18. Al Nofal AA, Altayar O, BenKhadra K, et al. Bone turnover markers in Paget's disease of the bone: A Systematic review and meta-analysis. *Osteoporos Int*. Jul 2015; 26(7): 1875-91. PMID 26037791
19. Martlı HF, Saylam B, Er S, et al. Evaluation of preoperative procollagen type 1 N-terminal peptide and collagen type 1 C-telopeptide levels in the prediction of postoperative hypocalcemia in patients undergoing parathyroidectomy due to primary hyperparathyroidism. *Langenbecks Arch Surg*. Jan 31 2023; 408(1): 71. PMID 36720758
20. Rianon N, Alex G, Callender G, et al. Preoperative serum osteocalcin may predict postoperative elevated parathyroid hormone in patients with primary hyperparathyroidism. *World J Surg*. Jun 2012; 36(6): 1320-6. PMID 22278606
21. 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*. May 2020; 26(Suppl 1): 1-46. PMID 32427503
22. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. Oct 2022; 33(10): 2049-2102. PMID 35478046
23. 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*. May 01 2019; 104(5): 1595-1622. PMID 30907953
24. Shoback D, Rosen CJ, Black DM, et al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. *J Clin Endocrinol Metab*. Mar 01 2020; 105(3). PMID 32068863
25. Singer FR, Bone HG, Hosking DJ, et al. Paget's disease of bone: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. Dec 2014; 99(12): 4408-22. PMID 25406796
26. McCloskey EV, Vasikaran S, Cooper C, et al. Official Positions for FRAX® clinical regarding biochemical markers from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®. *J Clin Densitom*. 2011; 14(3): 220-2. PMID 21810528
27. Kendler DL, Compston J, Carey JJ, et al. Repeating Measurement of Bone Mineral Density when Monitoring with Dual-energy X-ray Absorptiometry: 2019 ISCD Official Position. *J Clin Densitom*. 2019; 22(4): 489-500. PMID 31378452
28. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause*. Sep 01 2021; 28(9): 973-997. PMID 34448749

29. U.S. Preventive Services Task Force (USPSTF). Osteoporosis to Prevent Fractures: Screening. June 2018 (updated in progress).
<https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/osteoporosis-screening>. Accessed December 9, 2024.
30. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Collagen Crosslinks, any Method (190.19). 2002; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=96&ncdver=1&DocID=190.19&SearchType=Advanced&bc=IAAABAAAAAA&>. Accessed December 9, 2024.
31. Rules and Regulations: Medicare National Coverage Decision for Collagen Crosslinks, Any Method Other Names/Abbreviations. Federal Register. 2001;66(226):58843-58844.