

Bone Turnover Markers Testing

Policy Number: AHS - G2051 – Bone Turnover Markers Testing	Prior Policy Name and Number, as applicable: <ul style="list-style-type: none"> • AHS - G2051 – Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated with High Bone Turnover
Original Effective Date: 05/15/2022 Current Effective Date: 01/01/2025	

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I. Policy Description

Bone metabolism involves a continual, dynamic equilibrium between bone growth and resorption. Bone turnover markers (BTMs) are biochemical markers for assessment of bone formation or bone resorption. These markers may be useful in determining risk of fracture and bone loss (Rosen, 2023b).

II. Related Policies

Policy Number	Policy Title
AHS-G2005	Vitamin D Testing
AHS-G2164	Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document. *Bone turnover markers are listed in Note 1.*

- 1) For individuals treated with bisphosphonates, measurement of bone turnover markers to assess an individual’s compliance with bisphosphonate therapy or for fracture risk prediction **MEETS COVERAGE CRITERIA** at the following intervals:
 - a) To establish baseline levels before initiating bisphosphonate treatment
 - b) Every three months after initiation or change of therapy for the first year.
 - c) Every two years when no medication changes have occurred.

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- 2) For individuals with osteoporosis, measurement of bone turnover markers to monitor teriparatide treatment **DOES NOT MEET COVERAGE CRITERIA.**

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual’s illness.

- 3) As a diagnostic test for osteoporosis, measurement of bone turnover markers **DOES NOT MEET COVERAGE CRITERIA.**
- 4) In the diagnosis and management of patients with other conditions associated with high rates of bone turnover, measurement of bone turnover markers **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

Note 1: Bone turnover markers include (Rosen, 2023a, 2023b; Talwar, 2024):

- 1. Bone formation markers
 - a. Serum bone-specific alkaline phosphatase (BSAP/BALP)
 - b. Serum osteocalcin (OC)
 - c. Serum type 1 procollagen (C-terminal/N-terminal): C1NP or P1NP
- 2. Bone resorption markers
 - a. Urinary hydroxyproline (HYP)
 - b. Urinary total pyridinoline (PYD)
 - c. Urinary free deoxypyridinoline (DPD)
 - d. Urinary or serum collagen type 1 cross-linked N-telopeptide (NTX)
 - e. Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)
 - f. Bone sialoprotein (BSP)
 - g. Serum Tartrate-resistant acid phosphatase 5b (TRACP5b)
 - h. Cathepsin K

IV. Table of Terminology

Term	Definition
AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
AFOS	Asian Federation of Osteoporosis Societies
ALP	Alkaline phosphatase
B-ALP	Bone-specific alkaline phosphatase
BAP	Bone-specific alkaline phosphatase
BMA	Bone marker assays
BMD	Bone mass density
BMD	Bone mineral density
BP	Bisphosphonates
BSAP/BALP	Bone-specific alkaline phosphatase specific to osteoblasts

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BSP	Bone sialoprotein
BTMs	Bone turnover markers
C1NP or P1NP	Type 1 procollagen (C-Terminal/N-Terminal)
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease–mineral and bone disorder
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CTX	C-CT terminal telopeptide of type I collagen
CV	Coefficient of variation
DEXA	Dual energy x-ray absorptiometry
DPD	Deoxypyridinoline
ELISA	The enzyme-linked immunosorbent assay
ESCEO	Economic aspects of osteoporosis and osteoarthritis
FDA	Food and Drug Administration
FRAX	Fracture Risk Assessment Tool
GR	Gradient of risk
HYP	Hydroxyproline
ICTP	Serum c-terminal cross-linked telopeptide of type I collagen
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IOF	International Osteoporosis Foundation
ISCD	International Society for Clinical Densitometry
KDIGO	Kidney disease improving global outcomes
LDTs	Laboratory-developed tests
LSC	Least significant change
NAMS	North American Menopause Society
NOGG	National Osteoporosis Guideline Group
NTX	N-telopeptide
NTX	Cross-linked n-telopeptides of type 1 collagen
OC	Osteocalcin
PDB	Paget's disease of bone
PHPT	Primary hyperparathyroidism
P1CP	Carboxy terminal propeptide
P1NP	Procollagen type I n propeptide
PTH	Parathyroid hormone
PYD	Pyridinoline
RACGP	Royal Australian College of General Practitioners
ROS	Royal Osteoporosis Society
s-CTX	Serum c-terminal cross-linking telopeptide of type I collagen
s-PINP	Serum procollagen type I N propeptide
TH	Total hip
TRACP-5b/TRAP-5B	Tartrate-resistant acid phosphatase 5b
USPSTF	United States Preventative Services Task Force
βCTX-I	Bone alkaline phosphatase for bone formation and c-terminal cross-linking telopeptide of type I collagen

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V. Scientific Background

The resorption and reformation of bone are normally tightly regulated and coupled so that bone mass does not change. Bone disease occurs when these processes are uncoupled (Rosen, 2023a, 2023b). Biomarkers involved in the processes of resorption or formation have been proposed as measures for prediction of future bone loss, fracture risk, and more. Resorption markers include pyridinium crosslinks (PYD, DPD), C- and N-telopeptides (CTX, ICTP, NTX), tartrate-resistant acid phosphatase (TRACP) 5b, and cathepsin K, while formation markers include procollagen type I propeptides (PICP, PINP), osteocalcin, and bone-specific alkaline phosphatase (BSAP, also known as BALP) (Rosen, 2023a, 2023b).

Formation markers are characteristic of bone formation rate. PICP and PINP are carboxy- and amino-sides of the tropocollagen peptide, which is a precursor to type I collagen in bone. The serum concentration of these peptides reflects synthesis of new collagen. Osteocalcin is a component of osteoid, and BSAP is the alkaline phosphatase specific to osteoblasts. These biomarkers reflect the activity of osteoblasts. Of these markers, BSAP and PINP are considered the most clinically useful (Rosen, 2023a, 2023b).

Resorption markers are characteristic of bone resorption rate (breakdown of bone). Pyridinium crosslinks are components of bone collagen, C- and N- telopeptides are crosslinks between bone collagen molecules, TRACP is anchored to the osteoclasts that initiate bone resorption, and cathepsin K is involved in digestion of the organic matrix (Manolagas, 2024; Rosen, 2023a, 2023b). Of these markers, urinary NTX and serum CTX are considered the most clinically useful (Rosen, 2023a, 2023b).

The measurement and use of these biomarkers remain complicated. Biologic variability between and within patients is significant, as factors such as age, gender, body mass index, circadian rhythms, menstruation, smoking, time of food consumption, exercise, and more may influence the levels of BTMs (Rosen, 2023a, 2023b). Moreover, assays used to measure these biomarkers vary considerably, as both urinary and serum samples have been used. Lack of standardization has limited the use of BTMs in the clinical setting (Rosen, 2023a, 2023b).

Vitamin D supplementation has been used in the past for musculoskeletal diseases in both a prevention and treatment capacity— but data on supplementation with vitamin D and any corresponding effects on bone resorption and formation has been inconclusive. One study that investigated the effects of vitamin D supplementation on bone turnover markers such as bone-specific alkaline phosphatase (bALP), osteocalcin (OC), C-terminal telopeptide (CTX), and procollagen type 1 N-terminal propeptide (P1NP) failed to show any significant impact of vitamin D on bone turnover markers (Schwetz et al., 2017), while another study noted “a small, but significant, decrease in the bone formation marker procollagen of type 1 amino-terminal propeptide (P1NP)—in the vitamin D group as compared to the placebo group” (Jorde et al., 2019).

Analytical Validity

Eastell et al. (2000) assessed the biological variability between serum and urinary N-telopeptides of type I collagen (NTX). A total of 277 postmenopausal individuals were included, and urine and serum specimens were included to identify short-term variability. Long-term variability was

determined by comparing NTX at baseline and at two months. The authors found the median short-term coefficient of variation (CV) was 13.1% for urinary NTX and 6.3% for serum NTX. Long-term CV% was found to be 15.6% for urinary NTX and 7.5% for serum NTX. The authors also observed that to be 90% confident that a decrease in NTX after antiresorptive therapy was not caused by variability alone, a 31% decrease in urinary NTX and a 14% decrease in serum NTX are needed (Eastell et al., 2000).

Seibel et al. (2001) described the results of an international proficiency testing program for biochemical bone markers among clinical laboratories. The authors sent out two urinary and two serum pools (both normal and increased concentrations of markers) to 79 laboratories. The CVs were as follows: “serum bone-specific alkaline phosphatase (n = 47 laboratories), 16–48%; serum osteocalcin (n = 31), 16–42%; urinary free deoxypyridinoline (n = 30), 6.4–12%; urinary total deoxypyridinoline and pyridinoline (n = 29), 27–28%; urinary N-terminal cross-linked telopeptide of type I collagen (n = 10), 39%; serum C-terminal cross-linked telopeptide of type I collagen (ICTP; n = 8), 22–27%; urinary hydroxyproline (n = 13), 12%”. The authors concluded that “even with identical assays and methods, results for most biochemical markers of bone turnover differ markedly among laboratories” (Seibel et al., 2001).

Schafer et al. (2010) assessed the laboratory reproducibility of urine N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP). The authors obtained serum and urine from five postmenopausal individuals and sent specimens to six labs over eight months. They found that “Longitudinal coefficients of variation (CVs) ranged from 5.4% to 37.6% for NTX and from 3.1% to 23.6% for BAP. Within-run CVs ranged from 1.5% to 17.2% for NTX” (Schafer et al., 2010).

Hlaing and Compston (2014) notes that “although automated platforms have substantially improved the analytical variability of bone turnover markers, reproducibility still varies substantially”. The National Bone Health Alliance executed a project to standardize bone turnover marker collection procedures and reduce pre-analytical variability (Bauer et al., 2012). The results of that project and the IOF and IFCC Bone Marker Standards Working Group identification of PINP and CTX-I in blood to be the reference markers of bone turnover for the fracture risk prediction and monitoring of osteoporosis treatment (Vasikaran et al., 2011) have resulted in recommendations for standard sample handling and patient preparation (Szulc et al., 2017). Standardization and harmonization of clinical assays for bone turnover markers such as CTx and P1NP are ongoing (IFCC, 2020).

Clinical Utility and Validity

Johansson et al. (2014) performed a meta-analysis to “examine the performance characteristics of serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) in fracture risk prediction in untreated individuals in prospective cohort studies.” Six studies were included. The authors identified a “significant” association between s-CTX and risk of fracture (gradient of risk [GR] = 1.18). The hazard ratio per standard deviation increase in s-PINP was found to be 1.23 and was unadjusted for bone mineral density. The association between s-CTX and fracture risk was found to be 1.23. The authors concluded that “there is a modest but significant association between BTMs and risk of future fractures” (Johansson et al., 2014).

Marques et al. (2016) “assessed whether circulating bone formation and resorption markers (BTM) were individual predictors for trabecular and cortical bone loss, periosteal expansion, and fracture risk in older adults aged 66 to 93.” A total of 1069 participants were included in the study. Bone formation was assessed by serum procollagen type I N propeptide (PINP) and osteocalcin, and bone resorption was assessed by C-terminal cross-linking telopeptide of type I collagen (CTX). Inter-assay coefficients of variation were <3% for all BTM. A total of 236 participants sustained a fracture during the median follow-up of 11.7 years. The authors found that “increase in BTM levels was associated with faster cortical and trabecular bone loss at the femoral neck and proximal femur. Higher BTM levels were positively related with periosteal expansion rate at the femoral neck in men. Markers were not associated with fracture risk” (Marques et al., 2016).

Mederle et al. (2018) investigated the correlation between bone mass density (BMD) and “serum levels of BTMs (tartrate-resistant acid phosphatase-5b [TRAP-5b]), bone-specific alkaline phosphatase (BSAP), in postmenopausal osteoporotic individuals as compared to healthy postmenopausal subjects.” A total of 132 postmenopausal individuals with osteoporosis were included along with 81 healthy postmenopausal individuals. BSAP was found to have a sensitivity of 76.5% and specificity of 84.3% at a cutoff of 21.27 U/L, and TRAP-5b was found to have a sensitivity of 86.3% and specificity of 90.6% at a cutoff of 3.45 U/L. The authors concluded that “our study showed that BMD correlates negatively with BTMs and TRAP-5b presents a good specificity in identifying patients with postmenopausal osteoporosis” (Mederle et al., 2018).

Tian et al. (2019) performed a meta-analysis “to explore whether bone turnover biomarkers (BTMs), i.e., C-terminal telopeptide of type I collagen (CTX) and procollagen type I aminoterminal propeptide (PINP), are associated with fracture.” Nine studies were included. PINP had a “significant” positive association with fracture (adjusted gradient risk [GR] = 1.28) after adjusting for confounders. CTX was also seen to associate with fracture (GR = 1.20). The authors concluded, “Our results indicate a statistically significant but modest association between BTMs (s-PINP or s-CTX) and future fracture risk after adjusting for BMD and clinical risk factors. The causal relationship between the two clinical conditions requires future validation with more standardized studies” (Tian et al., 2019).

Naylor et al. (2019) evaluated bone turnover markers (BTMs) ability to monitor “offset of treatment with bisphosphonates (BP) in osteoporosis.” This was done by comparing the changes in BTMs and total hip (TH) bone mineral density (BMD). CTX and PINP were the BTMs analyzed, and offset was defined by “an increase greater than the least significant change (LSC) and an increase above the reference mean value.” Fifty individuals were included, and at 48 weeks after stopping BPs, “CTX was greater than the LSC for 66% of the participants and PINP 72%; CTX was above the reference mean for 64% of the participants and PINP 42%.” The authors also found that the decrease in TH-BMD was greater for those with the largest increases in BTMs, compared to those with “continued suppression.” The authors concluded that “The measurement of BTM after withdrawal of BPs is potentially useful to evaluate patients that are taking a pause from treatment. An increase in BTMs more than the LSC and/or reference mean reflects loss of treatment effect and identifies patients that are likely to have a decrease in BMD” (Naylor et al., 2019).

Massera et al. (2019) evaluated the associations of osteocalcin (OC) and C-telopeptide of type I collagen (CTX) with “long-term incidence of hip fracture” in post-menopausal individuals. A total of 1680 individuals from the population-based Cardiovascular Health Study were included, and over a median follow-up period of 12.3 years, 288 hip fractures occurred. The authors found that increasing levels of CTX up to the middle-upper range (hazard ratio = 1.52 per standard deviation increase), with increases past this range only incrementally increasing risk (hazard ratio = 0.8). The authors identified an “inverted U-shaped relationship with incident fracture after adjustment” when comparing quartiles to each other, and an association was only seen for the quartile three to quartile one comparison (hazard ratio = 1.63). In a subset with “available measures,” both OC and CTX were “inversely associated with bone mineral density of the hip.” The authors concluded that “CTX, but not OC, levels were associated with incident hip fracture in post-menopausal individuals, a relationship characterized by an inverted U-shape” (Massera et al., 2019).

Migliorini et al. (2021) performed a systematic review of clinical trials reporting data on biomarkers for postmenopausal osteoporosis. A total of 36,706 patients were included from randomized trials. Data on biomarkers and clinical outcomes such as BMD, t-score, rate of fractures and adverse events were analyzed. Authors found that greater values of bone alkaline phosphatase (bALP) were associated with more vertebral and non-vertebral fractures. Greater values of urinary cross-linked N-telopeptides of type I collagen (NTx) at baseline were linked with an increase in adverse events at the last follow-up, and greater values of C-telopeptide of type I collagen at baseline were associated with more adverse events leading to discontinuation, gastrointestinal adverse events, musculoskeletal adverse events, and mortality. The authors concluded that the review “supports the adoption of BMTs during pharmacological therapy setting of patients suffering from osteoporosis” (Migliorini et al., 2021).

Wei et al. (2021) explored the relationship of procollagen type one N-terminal peptide (P1NP) and β cross-linked C-telopeptide of type one collagen (β -CTX) with bone mineral density (BMD) in postmenopausal individuals. All postmenopausal subjects “were selected from a community-based case-control study and P1NP and β -CTX were also collected and tested. The main correlation analysis was applied to explore the relationships of BMD, P1NP, and β -CTX.” The results indicated that of the 1055 post-menopausal participants that were enrolled, “the BMD at all sites kept a decrease continually with age ($P < 0.01$). In addition, the level of β -CTX increased significantly from 45 to 50 years old and remained at a high level in the later stage, while the level of P1NP changed little or even decreased with age. Logistic regression model showed that β -CTX has better ability to predict BMD than P1NP, as demonstrated by an area under the curve (AUC) of 0.63.” In conclusion, P1NP and β -CTX are important markers to monitor bone metabolism (Wei et al., 2021).

VI. Guidelines and Recommendations

The Bone Health and Osteoporosis Foundation

In 2022, The Bone Health and Osteoporosis Foundation updated their guideline for the prevention and treatment of osteoporosis. Regarding biochemical markers of bone turnover, the guideline states:

Biochemical markers of bone turnover may:

- Predict rapidity of bone loss in untreated postmenopausal individuals.
- “Predict extent of fracture risk reduction when repeated after 3—6 months of treatment with FDA-approved therapies.
- Predict magnitude of BMD increases with FDA-approved therapies.
- Characterize patient compliance and persistence with osteoporosis therapy using a serum CTX for an antiresorptive medication and PINP for an anabolic therapy (least significant change [LSC] is approximately a 40% reduction in CTX).
- Potentially be used during a bisphosphonate holiday to suggest when medication should be restarted, although more data are needed to support this recommendation”(LeBoff et al., 2022).

The North American Menopause Society (NAMS)

In 2021, the North American Menopause Society (NAMS) issued an updated position on the management of osteoporosis in postmenopausal individuals. NAMS stated:

“Bone turnover markers cannot diagnose osteoporosis and have varying ability to predict fracture risk in clinical trials. Bone turnover markers have been used primarily in clinical trials to demonstrate group responses to treatment” (NAMS, 2021).

“Although used by some osteoporosis specialists, the routine use of bone turnover markers in the evaluation of patients with osteoporosis is not recommended” (NAMS, 2021).

“Although changes in bone turnover markers are used by some specialists to assess adherence and effectiveness of therapy, routine use of bone markers is not recommended” (NAMS, 2021).

International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

In 2021, the IOF/IFCC published “*Practical Considerations for the Clinical Application of Bone Turnover Markers in Osteoporosis*”(Vasikaran et al., 2023). The authors concluded, “Serum PINP and β -CTX are useful for monitoring oral therapy in osteoporosis. Further studies for their application in managing offset of drug action after cessation of antiresorptive therapies with bisphosphonates and denosumab would be useful. Large-scale fracture risk prediction studies of PINP and β -CTX in various untreated population groups to assess how they interact with established risk factors used in risk calculators such as FRAX may help to include BTMs in such algorithms.

The B-ALP and TRACP-5b are least affected by renal failure and may be of potential use in assessment for osteoporosis in patients with CKD and monitoring such patients when treated. Studies of utility of TRACP-5b and B-ALP in fracture risk assessment as well as monitoring therapy and assessing offset of treatment effect in osteoporosis patients with CKD stages 3a-5D is warranted.

From an analytical point of view, standardization or harmonization of commercial assays for BTMs is important for collation of data from different studies and uniform application of decision limits and treatment targets in clinical guidelines. IOF-IFCC C-BM is pursuing these activities” (Vasikaran et al., 2023).

American Association of Clinical Endocrinologists and American College of Endocrinology

An update to the 2016 Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis was published in 2020. In it, the AACE/ACE state “Consider using bone turnover markers in the initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk”, which is identical to the 2016 statement, but the 2020 edition is graded at an “A”, up from “B” in 2016.

Similarly, the statement “Consider using bone turnover markers (BTMs) for assessment of patient compliance and efficacy of therapy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction, and significant increases indicate good response to anabolic therapy” remains unchanged from the 2016 version, which was given a grade B.

Other relevant recommendations include:

- “Consider bone turnover markers at or below the median value for premenopausal [individuals] as a target for response to therapy for patients taking antiresorptive agents. Consider significant increases in bone formation markers as a pharmacologic response to anabolic therapy.”
- “The ending of a bisphosphonate holiday should be based on individual patient circumstances such as... an increase in bone turnover markers.”

Overall, although the joint guidelines acknowledge that BTMs cannot diagnose osteoporosis, they note that “elevated levels can predict more rapid rates of bone loss” and “are associated with increased fracture risk independent of BMD [bone mineral density] in some studies”. Further, automated immunoassays have improved BTMs’ reproducibility, and “changes in markers have been associated with bone response to therapy and reduction of fracture risk”. Despite the numerous analytical issues with BTM assessment (lack of standardization, high cost, et al.), the guidelines note that some experts routinely use BTMs in clinical practice. They also note that the preferred bone turnover markers are PINP for bone formation and CTX for bone resorption. And, in the situations when patients might experience renal insufficiency or when there are insurance issues, then bone-specific alkaline phosphatase may be used. The guidelines conclude that “BTMs are useful in certain situations, such as assessment of fracture risk and to provide early feedback to patients that their drug is or is not working, which leads to discussions pertaining to medication compliance, drug absorption, and/or therapeutic efficacy. BTMs do not need to be assessed in all osteoporosis patients” (Camacho et al., 2020).

Consensus Group Report, managed by Scientific Advisory Board of European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases

This working group was intended to “to provide guidance to clinicians on how to use BTMs in patient evaluation in postmenopausal osteoporosis, in fracture risk prediction and in the monitoring of treatment efficacy and adherence to osteoporosis medication.” Their conclusions are listed below (Lorentzon et al., 2019):

- “The bone formation marker serum PINP [N-terminal collagen type I extension propeptide] and resorption marker serum β CTX-I [bone alkaline phosphatase for bone formation and C-terminal cross-linking telopeptide of type I collagen] are the preferred markers for evaluating bone turnover in the clinical setting.”
- “Bone turnover markers cannot be used to diagnose osteoporosis but can be of value in patient evaluation and can improve the ability to detect some causes of secondary osteoporosis.”
- “Serum β CTX-I and PINP correlate only moderately with bone loss in postmenopausal [individuals] and with osteoporosis medication-induced gains in BMD. Therefore, the use of bone turnover markers cannot be recommended to monitor osteoporosis treatment effect in individual patients.”
- “Adding data on serum β CTX-I and PINP levels in postmenopausal [individuals] can only improve fracture risk prediction slightly in addition to clinical risk factors and BMD and therefore has limited value.”
- “Bisphosphonates are the most commonly used osteoporosis medications, but adherence to oral bisphosphonates falls below 50% within the first year of treatment. Monitoring PINP and β CTX-I is effective in monitoring treatment adherence and can be defined as the sufficient suppression of these markers (by more than the LSC or to the lower half of the reference interval for young and healthy premenopausal [individuals]).”

The guideline remarks “It is possible that monitoring the bone marker response may aid in the use of bisphosphonate treatment frequency and dosing when denosumab treatment is stopped.”

The guideline also notes that a “systematic review of the present evidence concluded that there is insufficient evidence to recommend the use of monitoring bone turnover markers for predicting the effect of teriparatide treatment effect” (Lorentzon et al., 2019).

U.S. Preventative Services Task Force (USPSTF)

The 2018 USPSTF recommendation on screening to prevent osteoporotic fractures address clinical risk assessment and bone density measurement but do not mention bone turnover markers (Viswanathan et al., 2018).

Endocrine Society

The Endocrine Society released a guideline concerning pharmacological management of osteoporosis in postmenopausal individuals, which noted, “Monitoring bone turnover markers (serum C-terminal crosslinking telopeptide for antiresorptive therapy or procollagen type 1 N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy” (Eastell et al., 2019).

The Endocrine Society published an update to the above guideline in 2020, and the above statement concerning monitoring of bone turnover markers remained in the 2020 edition (Shoback et al., 2020).

The Endocrine Society also released guidelines regarding the management of Paget's Disease. They recommended "that in patients with increased bone turnover, biochemical follow-up should be used as a more objective indicator of relapse than symptoms" (Singer et al., 2014).

"For most patients, measurement of total alkaline phosphatase or other baseline disease activity markers at six to 12 weeks, when bone turnover will have shown a substantial decline, is an acceptable and cost-effective option" (Singer et al., 2014).

National Osteoporosis Guideline Group

The NOGG notes bone turnover markers (e.g., CTX, P1NP) as a possible measure to evaluate during investigation of osteoporosis/ fragility fractures (NOGG, 2021).

Kidney Disease Improving Global Outcomes (KDIGO): Mineral and bone disorder

The KDIGO released guidelines pertaining to bone turnover related to CKD.

- "In patients with CKD [stages] G3a–G5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover."
- "In patients with CKD [stages] G3a–G5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline)" (KDIGO, 2017).

The **Renal Association** also published a "commentary" on the KDIGO guidelines in 2018. In it, they remarked that "Although iPTH, whole PTH, and bALP levels were associated with bone turnover, no biomarker singly or in combination was sufficiently robust to diagnose low, normal, and high bone turnover in an individual patient [on dialysis]" (Burton et al., 2018).

Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism

This workshop published guidelines regarding management of asymptomatic primary hyperparathyroidism (PHPT). They note bone turnover markers as an optional measurement of asymptomatic PHPT, listing "bone-specific alkaline phosphatase activity, osteocalcin, P1NP; serum CTX, urinary NTX" (Bilezikian et al., 2014).

International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

The IOF/ESCEO issued joint guidelines stating the following (Kanis et al., 2018):

"Bone markers (serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) as markers of bone formation and bone resorption,

respectively) have some prognostic significance for fracture in situations where bone mineral density (BMD) is unavailable.”

The joint guidelines also note that if harmonization efforts for other bone turnover markers are successful, these markers may see use for fracture risk. Procollagen I N-terminal peptide (P1NP) and C-telopeptide breakdown products (especially serum CTX) are considered the most informative biochemical markers for monitoring of osteoporosis (Kanis et al., 2018).

International Osteoporosis Foundation (IOF), Asian Federation of Osteoporosis Societies (AFOS), and the International Society for Clinical Densitometry (ISCD)

The IOF Capture the Fracture program facilitates the establishment of Fracture Liaison Services (FLS) with a goal “properly identify and treat patients with fragility fractures, improve quality of post-fracture care, adherence, and prevention of secondary fractures worldwide, including the [Asia-Pacific] region.” In 2021, the IOF, AFOS, and ISCD endorsed a consensus statement on the use of BTMs in the Asia-Pacific region. They made the following consensus statements (Wu et al., 2021):

- “Endorse the use of BTMs, especially CTX and P1NP, as short-term monitoring tools for osteoporosis treatment, consistent with recommendations of the AACE/ACE, IOF, IFCC, JOS, NOF, TOA, and associated organizations.
- BTMs can be used to differentiate patients with relatively higher or lower bone turnover rates and thereafter, helping clinicians to choose an appropriate anti-osteoporosis treatment regimen.
- BTMs can reflect the therapeutic responses to anti-osteoporosis therapies earlier than BMD and are therefore of help both in selecting osteoporosis treatment and in assessing its responses to therapies.
- Absolute values or the degree of change from baseline for BTMs can be used to monitor the efficacy of osteoporosis therapies clinically.
- CTX and/or P1NP can be used to evaluate patient adherence and drug responses to anti-resorptive agents, with measurements suggested at baseline, three months, six months, and 12 months after starting treatment.
- P1NP can be used to evaluate patient adherence and drug responses to anabolic agents, with measurements at baseline, one to three months, six months, and 12 months after starting anabolic treatment.
- Encourage reimbursement of BTMs by different health insurance programs in the Asia-Pacific to improve patient adherence and treatment outcomes.
- Recommend appropriate use of BTMs as a short-term monitoring tool for improving the use of therapeutic regimens in osteoporosis care programs, such as fracture liaison service (FLS).”

They conclude that “the use of BTMs can be incorporated in treatment algorithms of osteoporosis care programs to improve patient adherence and treatment outcomes” (Wu et al., 2021).

The International Federation of Clinical Chemistry and Laboratory Medicine

In the most recent review of bone turnover markers for the journal of the International Federation of Clinical Chemistry and Laboratory Medicine the author Bhattoa (2018) found that “Although quite sensitive to a multitude of exogenous and endogenous pre-analytical factors, bone markers are best used in monitoring anti-osteoporosis therapy efficacy and compliance. Combination of BMD measurement by DEXA with biochemical markers of bone turnover levels, at least one bone resorption and one bone formation marker, may potentially improve early detection of individuals at increased risk for bone loss and eventually non-traumatic bone fracture. Furthermore, they have widespread clinical utility in osteoporosis, renal osteodystrophy, certain oncological conditions and rheumatic diseases” (Bhattoa, 2018).

International Society for Clinical Densitometry (ISCD)

The ISCD includes a comment on bone turnover markers in their guideline titled “Official Positions”, stating that “Serial BMD [bone mineral density] testing in combination with clinical assessment of fracture risk, bone turnover markers and other factors...can be used to determine whether treatment should be initiated in untreated patients, according to locally applicable guidelines” (ISCD, 2019).

Royal Australian College of General Practitioners (RACGP)

In 2013, the RACGP released a series of “Tests and results” aimed at providing information about common tests that general practitioners order regularly. The series focused on areas such as indications, what to tell the patient, what the test can and cannot tell you, and interpretation of the results. As an assessment of fracture risk, they note that “Bone turnover markers increase in proportion to fracture risk, independent of bone mineral density (BMD). In general, turnover markers also tend to be higher in patients with low bone density. However, this correlation is not absolute in individuals and this application of the test is most useful in population studies. Very high marker levels (more than 1.5 times the upper reference limit) are not typical of postmenopausal osteoporosis and should prompt a search for another cause. For example, after a fracture, markers may remain increased for up to six months. Other causes could include high turnover states such as hyperparathyroidism or hyperthyroidism, Paget disease, malignancy including myeloma, or advanced renal failure” (Coates, 2013).

As a method of monitoring the efficacy of osteoporosis treatment, BMD “is a common surrogate marker of osteoporosis treatment efficacy. However, due to the relatively small effect of treatment relative to the precision of the test, it is not practical to repeat BMD at intervals shorter than two years. Also, fracture risk reduction on treatment is far greater than would be predicted by the BMD increase achieved. Fewer than half of patients prescribed a bisphosphonate are taking the medication after 1 year. For these reasons, it is helpful to assess the effects of, and compliance with, treatment within a few months. Some studies show improved adherence to treatment when turnover marker results were provided to patients, although this finding is not universal” (Coates, 2013).

Overall, the RACGP’s guideline for osteoporosis management recognizes “the response of bone turnover markers to treatment, particularly in the first few months after initiating bisphosphonates or teriparatide, but does not yet recommend their routine use” (Coates, 2013).

Paget's Association, Guideline Development Group

This Guideline Development Group published a guideline titled “Diagnosis and Management of Paget's Disease of Bone in Adults”. The relevant remarks include (Ralston et al., 2019):

- “Serum total ALP [total alkaline phosphatase] is widely available and considerably cheaper than other biochemical markers that have been assessed in PDB [Paget's Disease of Bone].”
- “If total ALP values are normal and clinical suspicion of metabolically active PDB is high, measurement of BALP, PINP, or uNTX may be considered to screen for metabolically active disease.”
- “...elevations in markers of bone turnover occur in many disease states and cannot be used in isolation for the diagnosis of PDB.”
- “Measurement of PINP is recommended to predict lesion extent, as defined by scintigraphy, after bisphosphonate therapy.”
- “Measurement of biochemical markers of bone turnover are not recommended a means of predicting the response of bone pain to osteoclast inhibitors in PDB” (Ralston et al., 2019).

Royal Osteoporosis Society (ROS)

In 2021, the ROS updated a 2018 a statement on the use of bone markers and osteoporosis. In it, they included three reasons as to why bone markers may be used (Royal Osteoporosis Society, 2021):

- “a) To measure bone turnover as part of an assessment of bone strength and fracture risk. There haven’t been many research trials to prove how effective this is, so other methods are usually used to assess bone strength, including a bone density scan to measure your bone density, along with your other risk factors.
- b) To monitor the effectiveness of osteoporosis drug treatments. Most treatments work by slowing the rate of bone resorption. The rate of bone formation also slows, but the overall effect is that the two processes come back into balance, leading to improved bone strength. The effect of a drug treatment on bone turnover can be assessed using bone markers within six months of starting treatment.
- c) In research trials, to assess osteoporosis drugs in development. Although there is evidence to suggest the value of bone marker tests as outlined above, expert opinion is divided on how useful or necessary they are, and further research is required to establish how they should be best used in the management of osteoporosis.”

As to the recommendation on the use of bone markers, they noted that a “UK independent review in 2014, which looked at whether bone markers should be used to see if a drug treatment is working, concluded there was insufficient evidence available to make recommendations. International expert guidance, however, says that although more research is needed, bone markers can be useful in some situations” (Royal Osteoporosis Society, 2021).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Several tests for bone turnover markers have been cleared by the U.S. Food and Drug Administration (FDA) using the 510(k) process including the collagen cross-links tests: Osteomark® NTX Urine ELISA test from Abbott which measures cross-linked N-telopeptides of type 1 collagen (NTx), and Serum Crosslaps One-step ELISA test which measures hydroxyproline. Other bone turnover marker tests cleared through the FDA 510(k) process tests include: Access Ostase from Beckman Coulter which measures bone-specific alkaline phosphatase (B-ALP), N-MID Osteocalcin One-step ELISA from Osteometer Bio Tech (merged with Osteopro and now called Nordic Biotech) which measures osteocalcin (OC), and Elecsys® N-MID Osteocalcin Immunoassay (Roche Diagnostics).

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82523	Collagen cross links, any method
83500	Hydroxyproline; free
83505	Hydroxyproline; total
83937	Osteocalcin (bone gla protein)
84080	Phosphatase, alkaline; isoenzymes

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
01/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.
05/01/2024	<p>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review necessitated the following changes to coverage criteria:</p> <p>Removal of CC1: “1) For osteoporosis patients, measurement of bone turnover markers MEETS COVERAGE CRITERIA for the following situations:</p> <ul style="list-style-type: none"> a) In initial evaluation and management b) In fracture risk prediction” <p>BTM is recommended for fracture risk prediction in individuals who are receiving treatment for their osteoporosis.</p> <p>Adjustment of former CC2, now CC1, to address frequency of testing in individuals receiving bisphosphonate treatment. “1) For individuals treated with bisphosphonates, measurement of bone turnover markers to assess an individual’s compliance with bisphosphonate therapy MEETS COVERAGE CRITERIA at the following intervals:</p> <ul style="list-style-type: none"> a) To establish baseline levels before initiating bisphosphonate treatment b) Every three months after initiation or change of therapy for the first year. c) Every two years when no medication changes have occurred.” <p>All other CC except no CC3 edited for clarity and consistency.</p>

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03/10/2023	<p>Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria.</p> <p>All coverage criteria were edited for clarity and consistency.</p> <p>Added “Bone turnover markers are listed in Note 1.” Above CC and removed references to Note 1 in all CC</p>
05/15/2022	Initial Policy Implementation