

Bone Turnover Markers Testing

Policy Number: AHS - G2051 – Bone Turnover Markers Testing	Prior Policy Name and Number, as applicable:
Original Effective Date: 5/15/2022 Current Effective Date: 3/10/2023	

[POLICY DESCRIPTION](#) | [RELATED POLICIES](#) | [INDICATIONS AND/OR LIMITATIONS OF COVERAGE](#) | [TABLE OF TERMINOLOGY](#) | [SCIENTIFIC BACKGROUND](#) | [GUIDELINES AND RECOMMENDATIONS](#) | [APPLICABLE STATE AND FEDERAL REGULATIONS](#) | [APPLICABLE CPT/HCPCS PROCEDURE CODES](#) | [EVIDENCE-BASED SCIENTIFIC REFERENCES](#) | [REVIEW/REVISION HISTORY](#)

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, 2019b).

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 Section VII of this policy document

Bone turnover markers are listed in Note 1.

- 1) For osteoporosis patients, measurement of bone turnover markers **MEETS COVERAGE CRITERIA** for the following situations:
 - a) In initial evaluation and management
 - b) In fracture risk prediction

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

- 2) For individuals treated with bisphosphonates, measurement of bone turnover markers to assess patient compliance with bisphosphonate therapy **MEETS COVERAGE CRITERIA.**
- 3) For osteoporosis patients, 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 a patient's illness.

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

Note 1: Bone turnover markers include (Rosen, 2019a, 2019b; Talwar, 2020):

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
ALP	Alkaline phosphatase
BAP	Bone-specific alkaline phosphatase
BMA	Bone marker assays
BMD	Bone mass density
BMD	Bone mineral density
BP	Bisphosphonates

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Term	Definition
BSAP/BALP	Bone-specific alkaline phosphatase specific to osteoblasts
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
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
PICP	Carboxy terminal propeptide
P1NP	Procollagen type I n propeptide
PTH	Parathyroid hormone
PYD	Pyridinoline
s-CTX	Serum c-terminal cross-linking telopeptide of type I collagen
s-P1NP	Serum procollagen type I N propeptide
TH	Total hip
TRACP5b/TRAP-5B	Tartrate-resistant acid phosphatase 5b
USPSTF	United States Preventative Services Task Force

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Term	Definition
βCTX-I	Bone alkaline phosphatase for bone formation and c-terminal cross-linking telopeptide of type I collagen

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, 2019a, 2019b). 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, 2019a, 2019b).

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, 2019a, 2019b).

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, 2018; Rosen, 2019a, 2019b). Of these markers, urinary NTX and serum CTX are considered the most clinically useful (Rosen, 2019a, 2019b).

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, 2019a, 2019b). 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, 2019a, 2019b).

Analytical Validity

Eastell et al. (2000) assessed the biological variability between serum and urinary N-telopeptides of type I collagen (NTX). 277 postmenopausal women 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 2 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

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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 2 urinary and 2 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 women and sent specimens to six labs over 8 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 et al. (2018) notes that “although automated platforms have substantially improved the analytical variability of bone turnover markers, reproducibility still varies substantially” (Hlaing & Compston, 2014). 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, Eastell, 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, 2018).

Clinical Validity and Utility

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 for men and women and 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)

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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”. 1069 participants were included. 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 54 men and 182 women 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 in men and women. 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 women as compared to healthy postmenopausal subjects”. 132 postmenopausal women with osteoporosis were included along with 81 healthy postmenopausal women. 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 women were included, and at 48 weeks after stopping BPs, “CTX was greater than the LSC for 66% of women and PINP 72%; CTX was above the reference mean for 64% of women and PINP 42%.” The authors also found that the decrease in TH-BMD was greater for women 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).

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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 older women.” 1680 women 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 3 to quartile 1 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 women, 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. 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 1 N-terminal peptide (P1NP) and β cross-linked C-telopeptide of type 1 collagen (β -CTX) with bone mineral density (BMD) in postmenopausal women. “All postmenopausal women 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 women 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

National Osteoporosis Foundation

In 2014, the National Osteoporosis Foundation updated their guideline for prevention and treatment of osteoporosis (Cosman et al., 2014). Regarding biochemical markers of bone turnover, the guideline states:

Biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density.
- 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.
- Predict rapidity of bone loss.
- Help determine adequacy of patient compliance and persistence with osteoporosis therapy.
- Help determine duration of “drug holiday” and when and if medication should be restarted (Data are quite limited to support this use.)

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 women. 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 2011, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) published a position statement by a joint IOF-IFCC Bone Marker Standards Working Group (Vasikaran, Cooper, et al., 2011). The group’s overall conclusion was, “In summary, the available studies relating to bone turnover marker changes to fracture risk reduction with osteoporosis treatments are promising. Further studies are needed that take care of sample handling, ensure that bone turnover markers are measured in all available patients, and use the appropriate statistical methods, including an assessment of whether the final bone turnover marker level is a guide to fracture risk.”

American Association of Clinical Endocrinologists and American College of Endocrinology

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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 women 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:

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

- “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 women 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 women 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 women).”

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 (Viswanathan et al., 2018) address clinical risk assessment and bone density measurement but do not mention bone turnover markers.

Endocrine Society

The Endocrine Society released a guideline titled “*Pharmacological Management of Osteoporosis in Postmenopausal Women*”, 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).

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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 6 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 as a possible measure to evaluate during investigation of osteoporosis (NOGG, 2017).

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

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 [select one]; serum CTX, urinary NTX [select one]" (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:

"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."

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

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 (PINP) and C-telopeptide breakdown products (especially serum CTX) are considered the most informative biochemical markers for monitoring of osteoporosis (Kanis et al., 2018).

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

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).

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:

- “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).

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; pyrilinks test from Metra Biosystems which measures collagen type 1 cross-link, pyridium, Osteomark test from Ostex International which measures cross-linked N-telopeptides of type 1 collagen (NTx), and Serum Crosslaps One-step ELISA test which measures hydroxyproline. Other bone turnover cleared through the FDA 510(k) process tests include: Ostase from Beckman Coulter which measures bone-specific alkaline phosphatase (B-ALP), N-MID Osteocalcin One-step ELISA from Osteometer Bio Tech 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

Current Procedural Terminology® American Medical Association. All Rights Reserved.

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

- Bauer, D., Krege, J., Lane, N., Leary, E., Libanati, C., Miller, P., Myers, G., Silverman, S., Vesper, H. W., Lee, D., Payette, M., & Randall, S. (2012). National Bone Health Alliance Bone Turnover Marker Project: current practices and the need for US harmonization, standardization, and common reference ranges. *Osteoporos Int*, 23(10), 2425-2433. <https://doi.org/10.1007/s00198-012-2049-z>
- Bhattoa, H. P. (2018). Laboratory aspects and clinical utility of bone turnover markers. *Ejifcc*, 29(2), 117-128. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6053812/>
- Bilezikian, J. P., Brandi, M. L., Eastell, R., Silverberg, S. J., Udelsman, R., Marcocci, C., & Potts, J. T., Jr. (2014). Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. *The Journal of Clinical Endocrinology & Metabolism*, 99(10), 3561-3569. <https://doi.org/10.1210/jc.2014-1413>
- Burton, J. O., Goldsmith, D. J., Ruddock, N., Shroff, R., & Wan, M. (2018). Renal association commentary on the KDIGO (2017) clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD. *BMC Nephrology*, 19(1), 240. <https://doi.org/10.1186/s12882-018-1037-8>
- Camacho, P. M., Petak, S. M., Binkley, N., Diab, D. L., Eldeiry, L. S., Farooki, A., Harris, S. T., Hurley, D. L., Kelly, J., Lewiecki, E. M., Pessah-Pollack, R., McClung, M., Wimalawansa, S. J., & Watts, N. B. (2020). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS— 2020 UPDATE EXECUTIVE SUMMARY. *Endocrine Practice*, 26(5), 564-570. <https://doi.org/10.4158/GL-2020-0524>
- Cosman, F., de Beur, S. J., LeBoff, M. S., Lewiecki, E. M., Tanner, B., Randall, S., & Lindsay, R. (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*, 25(10), 2359-2381. <https://doi.org/10.1007/s00198-014-2794-2>
- Eastell, R., Mallinak, N., Weiss, S., Ettinger, M., Pettinger, M., Cain, D., Fressland, K., & Chesnut, C., 3rd. (2000). Biological variability of serum and urinary N-telopeptides of type I collagen in postmenopausal women. *J Bone Miner Res*, 15(3), 594-598. <https://doi.org/10.1359/jbmr.2000.15.3.594>
- Eastell, R., Rosen, C. J., Black, D. M., Cheung, A. M., Murad, M. H., & Shoback, D. (2019). Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, 104(5), 1595-1622. <https://doi.org/10.1210/jc.2019-00221>
- Hlaing, T. T., & Compston, J. E. (2014). Biochemical markers of bone turnover - uses and limitations. *Ann Clin Biochem*, 51(Pt 2), 189-202. <https://doi.org/10.1177/0004563213515190>
- IFCC. (2018). Chapter 8.3.50 Standardisation of Bone Marker Assays (WG-BMA) in collaboration with IOF. In E. Cavalier (Ed.), *IFCC Handbook-2018-2020*. <https://www.ifcc.org/media/477331/ifcc-handbook-2018-2020-chapter-08.pdf>
- ISCD. (2019). *2019 ISCD Official Positions – Adult*. <https://iscd.org/learn/official-positions/adult-positions/>

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

- Johansson, H., Oden, A., Kanis, J. A., McCloskey, E. V., Morris, H. A., Cooper, C., & Vasikaran, S. (2014). A meta-analysis of reference markers of bone turnover for prediction of fracture. *Calcif Tissue Int*, 94(5), 560-567. <https://doi.org/10.1007/s00223-014-9842-y>
- Kanis, J. A., Cooper, C., Rizzoli, R., & Reginster, J.-Y. J. O. I. V. (2018). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. (1), 3-44. <https://www.deepdyve.com/lp/springer-journals/european-guidance-for-the-diagnosis-and-management-of-osteoporosis-in-RAKeOAcgKm>
- KDIGO. (2017). KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). <https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf>
- Lorentzon, M., Branco, J., Brandi, M. L., Bruyère, O., Chapurlat, R., Cooper, C., Cortet, B., Diez-Perez, A., Ferrari, S., Gasparik, A., Herrmann, M., Jorgensen, N. R., Kanis, J., Kaufman, J. M., Laslop, A., Locquet, M., Matijevic, R., McCloskey, E., Minisola, S., . . . Cavalier, E. (2019). Algorithm for the Use of Biochemical Markers of Bone Turnover in the Diagnosis, Assessment and Follow-Up of Treatment for Osteoporosis. *Adv Ther*, 36(10), 2811-2824. <https://doi.org/10.1007/s12325-019-01063-9>
- Manolagas, S. (2018). Normal skeletal development and regulation of bone formation and resorption. In J. Mulder (Ed.), *UpToDate*. <https://www.uptodate.com/contents/normal-skeletal-development-and-regulation-of-bone-formation-and-resorption>
- Marques, E. A., Gudnason, V., Lang, T., Sigurdsson, G., Sigurdsson, S., Aspelund, T., Siggeirsdottir, K., Launer, L., Eiriksdottir, G., & Harris, T. B. (2016). Association of bone turnover markers with volumetric bone loss, periosteal apposition, and fracture risk in older men and women: the AGES-Reykjavik longitudinal study. *Osteoporos Int*, 27(12), 3485-3494. <https://doi.org/10.1007/s00198-016-3675-7>
- Massera, D., Xu, S., Walker, M. D., Valderrábano, R. J., Mukamal, K. J., Ix, J. H., Siscovick, D. S., Tracy, R. P., Robbins, J. A., Biggs, M. L., Xue, X., & Kizer, J. R. (2019). Biochemical markers of bone turnover and risk of incident hip fracture in older women: the Cardiovascular Health Study. *Osteoporos Int*, 30(9), 1755-1765. <https://doi.org/10.1007/s00198-019-05043-1>
- Mederle, O. A., Balas, M., Ioanoviciu, S. D., Gurban, C. V., Tudor, A., & Borza, C. (2018). Correlations between bone turnover markers, serum magnesium and bone mass density in postmenopausal osteoporosis. *Clin Interv Aging*, 13, 1383-1389. <https://doi.org/10.2147/cia.S170111>
- Migliorini, F., Maffulli, N., Spiezia, F., Peretti, G. M., Tingart, M., & Giorgino, R. (2021). Potential of biomarkers during pharmacological therapy setting for postmenopausal osteoporosis: a systematic review. *J Orthop Surg Res*, 16(1), 351. <https://doi.org/10.1186/s13018-021-02497-0>
- Naylor, K. E., McCloskey, E. V., Jacques, R. M., Peel, N. F. A., Paggiosi, M. A., Gossiel, F., Walsh, J. S., & Eastell, R. (2019). Clinical utility of bone turnover markers in monitoring the withdrawal of treatment with oral bisphosphonates in postmenopausal osteoporosis. *Osteoporos Int*, 30(4), 917-922. <https://doi.org/10.1007/s00198-018-04823-5>
- NOGG. (2017). Clinical guideline for the prevention and treatment of osteoporosis. <https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf>

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

- Ralston, S. H., Corral-Gudino, L., Cooper, C., Francis, R. M., Fraser, W. D., Gennari, L., Guañabens, N., Javaid, M. K., Layfield, R., O'Neill, T. W., Russell, R. G. G., Stone, M. D., Simpson, K., Wilkinson, D., Wills, R., Zillikens, M. C., & Tuck, S. P. (2019). Diagnosis and Management of Paget's Disease of Bone in Adults: A Clinical Guideline. *J Bone Miner Res*, 34(4), 579-604. <https://doi.org/10.1002/jbmr.3657>
- Rosen, H. (2019a). *Bone physiology and biochemical markers of bone turnover*. <https://www.uptodate.com/contents/bone-physiology-and-biochemical-markers-of-bone-turnover>
- Rosen, H. (2019b). *Use of biochemical markers of bone turnover in osteoporosis*. <https://www.uptodate.com/contents/use-of-biochemical-markers-of-bone-turnover-in-osteoporosis>
- Schafer, A. L., Vittinghoff, E., Ramachandran, R., Mahmoudi, N., & Bauer, D. C. (2010). Laboratory reproducibility of biochemical markers of bone turnover in clinical practice. *Osteoporos Int*, 21(3), 439-445. <https://doi.org/10.1007/s00198-009-0974-2>
- Seibel, M. J., Lang, M., & Geilenkeuser, W. J. (2001). Interlaboratory variation of biochemical markers of bone turnover. *Clin Chem*, 47(8), 1443-1450. <http://www.clinchem.org/cgi/pmidlookup?view=long&pmid=11468235>
- Shoback, D., Rosen, C. J., Black, D. M., Cheung, A. M., Murad, M. H., & Eastell, R. (2020). Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. *The Journal of Clinical Endocrinology & Metabolism*, 105(3), 587-594. <https://doi.org/10.1210/clinem/dgaa048>
- Singer, F. R., Bone, H. G., III, Hosking, D. J., Lyles, K. W., Murad, M. H., Reid, I. R., & Siris, E. S. (2014). Paget's Disease of Bone: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, 99(12), 4408-4422. <https://doi.org/10.1210/jc.2014-2910>
- Szulc, P., Naylor, K., Hoyle, N. R., Eastell, R., & Leary, E. T. (2017). 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*, 28(9), 2541-2556. <https://doi.org/10.1007/s00198-017-4082-4>
- Talwar, S. (2020). Bone Markers in Osteoporosis: Bone Turnover Markers, Bone Formation Markers, Bone Resorption Markers. *Medscape*. <http://emedicine.medscape.com/article/128567-overview>
- Tian, A., Ma, J., Feng, K., Liu, Z., Chen, L., Jia, H., & Ma, X. (2019). Reference markers of bone turnover for prediction of fracture: a meta-analysis. *J Orthop Surg Res*, 14(1), 68. <https://doi.org/10.1186/s13018-019-1100-6>
- Vasikaran, S., Cooper, C., Eastell, R., Griesmacher, A., Morris, H. A., Trenti, T., & Kanis, J. A. (2011). International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. *Clin Chem Lab Med*, 49(8), 1271-1274. <https://doi.org/10.1515/cclm.2011.602>
- Vasikaran, S., Eastell, R., Bruyere, O., Foldes, A. J., Garnero, P., Griesmacher, A., McClung, M., Morris, H. A., Silverman, S., Trenti, T., Wahl, D. A., Cooper, C., & Kanis, J. A. (2011). Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int*, 22(2), 391-420. <https://doi.org/10.1007/s00198-010-1501-1>

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

Viswanathan, M., Reddy, S., Berkman, N., Cullen, K., Middleton, J. C., Nicholson, W. K., & Kahwati, L. C. (2018). Screening to Prevent Osteoporotic Fractures: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama*, 319(24), 2532-2551. <https://doi.org/10.1001/jama.2018.6537>

Wei, X., Zhang, Y., Xiang, X., Sun, M., Sun, K., Han, T., Qi, B., Xie, Y., Zhang, R., & Zhu, L. (2021). Exploring the Relationship of Bone Turnover Markers and Bone Mineral Density in Community-Dwelling Postmenopausal Women. *Dis Markers*, 2021, 6690095. <https://doi.org/10.1155/2021/6690095>

X. Review/Revision History

Effective Date	Summary
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

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.