

# Collagen Crosslinks and Biochemical Markers of Bone Turnover (for Louisiana Only)

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[➔ Instructions for Use](#)

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## Application

This Medical Policy only applies to the state of Louisiana.

## Coverage Rationale

Serum or urine collagen crosslinks or biochemical markers are unproven and not medically necessary to assess risk of fracture, predict bone loss, or assess response to antiresorptive therapy.

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
82523	Collagen cross links, any method

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## Description of Services

Bone turnover markers are biochemical markers of either bone formation or bone resorption. Commercially marketed tests are available to assess some of these markers in urine and/or serum by high-performance liquid chromatography or immunoassay.

Even after growth is completed, bones are in a constant state of remodeling (or turnover), with initial absorption of bone by osteoclasts followed by deposition of new bone matrix by osteoblasts. This constant bone turnover is critical to the overall health of the bone by repairing microfractures and remodeling the bony architecture in response to stress.

Biochemical markers of bone turnover in the serum or urine are sometimes used to assess the risk of fracture, predict bone loss, or assess response to antiresorptive therapy. Biochemical markers such as pyridinoline, telopeptides, and urinary cross-linked N-telopeptide of type I collagen (which measure bone resorption) and osteocalcin and bone alkaline phosphatase (which measure bone formation) are obtained through serum and urine samples, making them a potentially attractive method for determining the risk of fracture and for the management of osteoporosis. Specifically, the information obtained could potentially be used to measure the rate of bone loss, assist in determining osteoporosis management, monitor changes in bone metabolism and density resulting from therapy, and manage osteoporosis therapy as needed for the individual. While these are frequently used in research studies, the use of biochemical markers in clinical practice is controversial because of (1) the complexity of interpreting the values for individuals, related to the intricacies inherent in bone metabolism, and (2) the lack of standardization, which has led to unacceptable levels of variation between processing laboratories.

## Clinical Evidence

The clinical validity of collagen crosslinks and bone turnover biomarkers are unproven since prospective well designed trials are needed to substantiate their role in managing decreased mineral bone density and improving clinical outcomes. There is insufficient clinical evidence for diagnosing osteoporosis or monitoring response to osteoporosis treatment; therefore, additional studies and clinical trials are needed to demonstrate their efficacy.

In a cross-sectional study Qu et al. (2025) sought to explore the relationship between bone turnover markers (BTMs) and bone mineral density (BMD) in the Chinese population. The study evaluated the relationship between BTMs and fracture risk in postmenopausal women and middle-aged and elderly men; and evaluated the role of BTMs in fracture risk prediction. A total of 580 participants (380 postmenopausal women and 200 men over the age of 50) were included in the study. BMD values were assessed for the lumbar spine, femoral neck, and total hip joint and biochemical indicators such as creatinine, type 1 procollagen N-terminal propeptide (P1NP), and beta cross-linked C-telopeptide of type 1 collagen ( $\beta$ -CTX). Furthermore, an online fracture risk assessment tool (FRAX) was used to calculate the probability of major osteoporotic fractures (PMOF) and hip fractures (PHF) over 10 years. The participants were divided into three groups based on the BMD T-score criteria: normal bone mass group (T-score  $\geq -1.0$  SD), osteopenic group ( $-2.5$  SD  $<$  T-score  $< -1.0$  SD), and osteoporotic group (T-score  $\leq -2.5$  SD). A comparison of differences in BTMs, BMD, and fracture risks among the three groups was performed. Additionally, differences in indicators between males and females and explored risk factors associated with BMD and fracture risk was evaluated. The study identified postmenopausal women showed higher bone turnover markers, osteoporosis prevalence, and fracture risks compared to men. A multivariate stepwise regression analysis identified P1NP was positively correlated with fracture risk for both PMOF ( $\beta = 0.087$ ,  $p = 0.005$ ) and PHF ( $\beta = 0.135$ ,  $p < 0.001$ ) over 10 years. In the logistic regression analysis, after adjusting for sex, the study found that for every standard deviation increase in P1NP, the future 10-year risk of fractures increased by approximately 5.2-fold in the high PMOF group and 5.6-fold in the high PHF group. The authors concluded that high serum P1NP levels were associated with increased fracture risk over a 10-year period. These findings suggested that serum P1NP measurement could be a valuable complementary tool alongside BMD measurements and FRAX assessments for identifying individuals at high risk of fracture. A few limitations were identified in the study. First, there was a lack of prospective cohort studies. Second, differences in parameters may not be accurate due to the limited sample size. Finally, the participants in the study were limited to one geographical area. Application of the findings would need to be verified in other geographical areas. Future studies with larger cohorts are needed to validate the findings.

Orford et al. (2024) conducted a randomized controlled trial (RCT) to measure the effects of antiresorptive agents on BTMs in critically ill women aged 50 years or older. BTMs and BMD were monitored for 1 year. Of 253 participants, 18 (nine were randomized to denosumab, seven to placebo, and two to zoledronic acid) were enrolled over 35 months before stopping the study due to the COVID-19 pandemic. Of the 18 participants, 10 (56%) completed the 1-year follow-up. The authors' findings showed that antiresorptive medications decreased the BTM type 1 cross-linked C-telopeptide (CTX) from days 0 to 28 by 43% compared with an increase of 26% observed with placebo. Mixed linear modeling revealed differences in the month after trial drug administration between the groups in serum CTX, alkaline phosphatase, parathyroid hormone, and phosphate. Change in BMD between the antiresorptive and placebo groups was not statistically analyzed due to a small sample size. No serious adverse events were reported. The authors concluded that in critically ill women aged 50 years or older, antiresorptive agents suppressed bone resorption markers without serious adverse events. Larger clinical trials in the critical illness setting should be conducted to define the efficacy and safety of antiresorptive agents and the effect on BMD and fracture over at least 1 year of follow-up. The limitations in the study include the small sample size, the limiting statistical analysis, and the interpretation of the results.

Yoo et al. (2023) conducted a study to investigate real-world data for CTX, P1NP, and osteocalcin through a multicenter clinical study and retrospectively analyzed the usefulness of BTMs in Korean participants. The selection criteria included pre- and postmenopausal participants with osteoporosis. Participant classifications included demographic characteristics

and BTM (CTX, P1NP, and osteocalcin) concentrations. The authors' findings showed that among women with no history of fractures, the level of P1NP (n = 2,100) was  $43.544 \pm 36.902$ , CTX (n = 1,855) was  $0.373 \pm 0.927$ , and osteocalcin (n = 219) was  $10.81 \pm 20.631$ . Among men with no history of fractures, the level of P1NP (n = 221) was  $48.498 \pm 52.892$ , CTX (n = 201) was  $0.370 \pm 0.351$ , and osteocalcin (n = 15) was  $7.868 \pm 10.674$ . Participants, both men and women, with osteoporosis treated with teriparatide had an increase in P1NP levels after 3 months, and a 50% increase was observed in women. Similarly, participants, both men and women, with osteoporosis treated with denosumab had decreased CTX levels after 3 months, with a reduction of 50% observed in women. The authors concluded that the results of this study can contribute to the specific evaluation of bone turnover status in the Korean population. In addition, the study provides P1NP levels in the Korean population for future comparative studies with other populations.

Voulgaridou et al. (2023) performed a review of RCTs to investigate the effects of vitamin D and calcium supplementation, separately and in combination, on bone density; circulating serum and blood plasma vitamin D, calcium, and parathyroid hormone (PTH) levels; markers of bone metabolism concentrations; and clinical outcomes, such as falls and osteoporotic fractures. Of 259 studies, 26 met the inclusion criteria. The authors' results identified that circulating 25(OH)D levels increased after vitamin D supplementation alone or in combination with calcium. Additionally, calcium with vitamin D supplementation but not vitamin D alone led to an increase in BMD, while no significant differences were documented for the reduction in the risk of total fractures. No significant changes were identified in circulating levels of plasma bone metabolism markers nor in the incidence of falls. In the groups receiving vitamin D and/or calcium supplementation, a decrease in blood serum PTH levels was observed. The authors concluded that vitamin D supplementation, alone or in combination with calcium, is considered fundamental in enhancing the positive effects of any therapy in individuals who are more fragile and at higher risk of vertebral and nonvertebral fragility fractures due to disorders related to bone metabolism (e.g., osteoporosis, vitamin D deficiency). However, further studies are needed to determine appropriate dosing regimens for the treatment of osteoporosis and the role of bone metabolism markers. The limitations identified are the short-duration studies, the small sample sizes, absence of a placebo comparator during the study period, gender bias, ethics-related differences, and vitamin D drug interactions.

Jia and Cheng (2022) conducted a study to investigate the correlation between risk factors of postmenopausal osteoporotic fracture, BMD, and BTMs; lipid metabolism; and body mass index (BMI). Data from 128 participants with postmenopausal osteoporotic fractures were collected. The Cox proportional hazards model was used to conduct univariate and multivariate analysis to screen the risk factors related to postmenopausal osteoporotic fractures. Blood samples were collected, which included blood lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), and immunodetection of biochemical markers of bone turnover (BMTs): serum cathepsin K, type II procollagen amino-terminal propeptide (PINP),  $\beta$ -collagen degradation products ( $\beta$ -CrossLaps), osteocalcin, and tartrate-resistant acid phosphatase. BMI of the survey participants was measured; BMD was detected, and its correlation with lipid metabolism was analyzed. The authors' results showed that the correlation study with lipid metabolism found that the smaller the BMI value and triglyceride level, the greater the BMD loss, exhibiting a downward trend. No significant correlation was observed between high-density lipoprotein cholesterol and low-density lipoprotein cholesterol content ( $p > 0.05$ ). Femoral neck and lumbar spine BMD were negatively correlated with cathepsin K, serum osteocalcin, PINP,  $\beta$ -CrossLaps, and tartrate-resistant acid phosphatase. The authors concluded that BMTs are highly expressed in postmenopausal women and increase with the decrease in bone density. Additionally, BMD severity, years since menopause, history of hysterectomy or ovariectomy, age, and number of deliveries are important risk factors for osteoporotic fractures. Further studies should be conducted due to limitations of a small sample size and participant age.

Borgen et al. (2022) completed a prospective cohort study to explore (1) cutoff values for P1NP and CTX that discriminate best participants' adherence to antiresorptive drugs (ARDs); (2) cutoff values for P1NP and CTX that best predict treatment effects in terms of BMD change; (3) whether P1NP and CTX predict fracture risk during follow-up of participants using and not using ARDs; and (4) variation in BTMs by time of day in participants using or not using ARDs. A total of 228 participants (82.2% women) were evaluated for ARD indication after a fragility fracture and were followed up for a mean of 4.6 years (SD, 0.5 years). BTM was measured at the 1-year and 2-year follow-ups. At baseline, 18 participants (9%) were already on an ARD, and an additional 140 started an ARD [alendronate (n = 121), denosumab (n = 15), or zoledronic acid (n = 22)]; hence, 158 participants (69%) had a prescribed ARD after baseline assessment, whereas 70 participants had no ARD prescribed because they did not have a treatment indication (T score  $> -1.5$  or FRAX score for major osteoporotic fracture  $< 20\%$ ). After the 2-year follow-up, 145 of 158 participants were still on an ARD [alendronate (n = 113), denosumab (n = 15), or zoledronic acid (n = 18)]. Nine participants died during the total observation time of 4.6 years, but no one died during the first 2 years of follow-up. The authors concluded that (1) P1NP and CTX levels below 30 and 0.25  $\mu\text{g/L}$  yielded the best discrimination between participants using or not using an ARD; (2) P1NP and CTX levels below 30 and 0.25  $\mu\text{g/L}$  yielded the best prediction for BMD gains after 2 years of ARD treatment; (3) P1NP can predict fractures in participants on ARDs; and (4) assessment of BTM can be extended to the whole day in participants on an ARD. Thus, BTMs constitute a valuable supplement to dual-energy X-ray absorptiometry (DXA) assessment of the effects of osteoporosis treatment and might replace DXA in some instances. However, DXA is still needed for decisions with respect

to diagnosis, assessment of treatment goals, and treatment pauses. Several limitations to this study exist. Participants in the group not using ARDs were healthier and younger and had no indication for ARDs. Fasting status was not ensured in the participants, and the BTMs were not measured at the same year of follow-up in all participants. The authors did not measure BTMs in the same participants at different time points in the day, and P1NP and CTX were measured using only the automated electrochemiluminescence immunoassays by Roche. Although the results are promising, the small sample size and lack of a comparison group limit the generalizability of the findings. Further research with RCTs is needed.

Slaven et al. (2022) conducted a case-control study to analyze changes in serum markers of bone turnover across multiple decades, specifically in women with osteoporosis compared with controls without osteoporosis, to determine the utility of serum markers of bone turnover as potential predictors of osteoporosis. The study consisted of a convenience sample of 20 individuals with osteoporosis and 20 control individuals matched by age and BMI. Serum samples were obtained from 20 women, who were diagnosed with osteoporosis after age 46 years, and 20 age-matched women with normal BMD from four time points in their lives (ages 25-31, 32-38, 39-45, and 46-60 years). Serum levels of BTMs [P1NP, parathyroid hormone, bone-specific alkaline phosphatase, osteocalcin, CTX, sclerostin, osteoprotegerin, osteopontin, and 25(OH)D] were measured using commercially available arrays and kits. Logistic regression was used to assess these individual serum markers as potential predictors of osteoporosis; mixed-effects modeling was then used to assess the change in BTMs between osteoporotic and control groups over time, and then five-fold cross-validation was performed to assess the classification ability of the models. Markers of bone turnover, bone-specific alkaline phosphatase, CTX, sclerostin, and osteocalcin were all independent predictors at multiple time points; osteopontin was an independent predictor in the 39- to 45-years age group. Receiver operating characteristic analyses demonstrated moderately strong classification ability at all time points. Sclerostin levels among groups diverged over time and were higher in the control group than the osteoporotic group, with differences observed at time points 3 and 4. The authors concluded that serum biomarker testing has the potential to serve as a screening tool that detects biochemical evidence of increased bone turnover at an age young enough to intervene meaningfully and prevent critical loss of bone mass. Although prospective validation is necessary before recommending widespread clinical use, this information may be used to identify individuals at risk for developing low BMD long before traditional screening would take place. This study was designed to test the early diagnostic capability of these biomarker profiles as they relate to osteoporosis; subsequent investigations must be performed with a larger number of individuals, and they should go through a validation process before clinical use. A small sample size ( $n = 20$ ) makes it difficult to decide whether these conclusions can be generalized to a larger population. Further investigation is needed before the clinical usefulness of this procedure is proven.

An RCT was performed by Stewart et al. (2022) to determine whether BTMs can be used as early markers of delayed fracture healing and the effect of vitamin D on BTM response after fracture. A total of 102 participants aged 18 to 50 years [median, 28 years (IQR, 23-35 years)], who were receiving an intramedullary nail for a tibial or femoral shaft fracture, were enrolled in an RCT comparing vitamin D<sub>3</sub> supplementation with placebo. Serum CTX (bone resorption marker) and P1NP (bone formation marker) were measured at baseline, 6 weeks, and 12 weeks post injury. Clinical and radiological fracture healing was assessed at 3 months. Results showed that CTX and P1NP concentrations peaked at 6 weeks in all groups. Elevated 6-week CTX and P1NP were associated with radiological healing at 12 weeks post injury (odds ratio, 10.5; 95% CI, 2.71-53.5;  $p = 0.002$ ). No association between CTX or P1NP and functional healing was observed. Baseline serum 25(OH)D showed a weak inverse relationship with P1NP ( $p = 0.036$ ) and CTX ( $p = 0.221$ ) at 12 weeks; however, the authors observed no association between vitamin D supplementation and either BTM. The authors stated that the association between 6-week BTM concentrations and 3-month radiological fracture healing, CTX, and P1NP showed these to be potential surrogate markers of fracture healing and concluded that CTX and P1NP concentrations increase during acute fracture healing. Limitations include that (1) unfasted blood draws were used, potentially introducing variability to the CTX measurements; (2) the sample included both tibia and femur fractures, potentially introducing variability to the BTM response; and (3) despite numerous contact attempts, attrition in the sample reached 35%. In addition, the short-term follow-up did not allow for assessment of intermediate- and long-term outcomes. Further investigation is needed before the clinical usefulness of this procedure is proven.

Li et al. (2021) conducted a cross-sectional study to identify the levels of serum periostin in Chinese postmenopausal women with different bone mass and the correlations between the periostin levels and the classical BTMs as well as BMD at different sites. A total of 331 Chinese postmenopausal women in Shanghai were enrolled in this study. Their clinical features were collected; their levels of serum periostin and traditional BTMs were measured by enzyme-linked immunosorbent assay or the fully automated immunoassay analyzer; and their BMD at different sites was measured by DXA. According to the T value of BMD, these postmenopausal women were divided into three groups: normal group ( $n = 84$ ), osteopenia group ( $n = 126$ ), and osteoporosis group ( $n = 121$ ). No difference was noted in the serum periostin levels among the above three groups of participants. Spearman correlation analysis revealed no correlation between the value of serum periostin and those of traditional BTMs and BMDs at different sites. The values of traditional BTMs were negatively correlated with those of BMDs at all measured sites. Furthermore, the receiver operating characteristic curves analysis indicated that among the periostin and traditional BTMs mentioned above, the best predictors for

postmenopausal osteoporosis in Chinese postmenopausal women in Shanghai were osteocalcin and P1NP (the areas under the ROC curve were 0.746 and 0.761, respectively). The authors concluded that serum periostin may not be used as a marker of systemic bone metabolism in Chinese postmenopausal women in Shanghai who do not have prior fracture. In addition, serum P1NP and osteocalcin levels may be the predictors of osteoporosis occurrence in Chinese postmenopausal women. Limitations to this study include a small and unequal number of postmenopausal women among the three groups. In addition, no follow-up was available to observe the changes in serum periostin, traditional BTMs, and BMD in postmenopausal women over time. Long-term evaluations of the results and prospective, randomized studies are still needed.

Ma et al. (2021) conducted a prospective RCT to investigate the clinical value of perioperative BTM monitoring to guide the treatment of osteoporosis in postmenopausal female participants after total knee arthroplasty from April 2017 to December 2018. The study included a total of 64 participants, divided into two groups: monitoring group (n = 32) and control group (n = 32). The participants were given oral medication (alendronate, calcitriol, and calcium) and followed up for 1 year. In the monitoring group, serum BTMs [C-telopeptide of type I collagen (CTX-I), PINP, and 25(OH)D] were assessed prior to operation and repeated post operation; alendronate was withdrawn when CTX-I and PINP reached the reference interval; and calcitriol and calcium were withdrawn when 25(OH)D reached the reference interval. In the control group, oral medication was implemented for a uniform duration of 3 months. During the 1-year follow-up, the mean maximum total point motion of the tibial component, BMD, visual analog scale score, range of motion, and Oxford Knee Score were obtained. In the monitoring group, BTM monitoring prolonged the medication duration but did not cause more adverse reactions than in the control group. The mean maximum total point motion values at 6 months and 12 months in the monitoring group were lower than those in the control group, and the BMD at 12 months in the monitoring group was significantly higher than that in the control group. Participants in the monitoring group had a lower visual analog scale score at 6 months and higher Oxford Knee Score at 6 months and 12 months than those in the control group. The authors concluded that the application of BTM monitoring to guide the treatment of osteoporosis can enhance bone density, maintain prosthesis stability, and improve surgical outcomes in postmenopausal female individuals with osteoporosis undergoing primary total knee arthroplasty. Limitations include a small sample size and short-term follow-up, which did not allow for assessment of long-term outcomes. In addition, several participants in the study were nonadherent to the follow-up and/or refused to provide blood samples post operation. Further research is needed to determine the clinical relevance of these findings.

A subanalysis of an RCT was performed by Curtis et al. (2021) to evaluate markers of maternal bone resorption, urinary CTX, influence of gestational vitamin D supplementation, and associations between CTX and maternal postnatal bone indices across pregnancy. The Maternal Vitamin D Osteoporosis Study (MAVIDOS) is a randomized, double-blinded, placebo-controlled trial of 1,000 IU cholecalciferol/d compared with placebo from 14 weeks of gestation to birth. Maternal second-void urinary  $\alpha$ - and  $\beta$ -CTX were measured (enzyme-linked immunosorbent assay) at 14 and 34 weeks of gestation; DXA was performed within 2 weeks postpartum. The Mann-Whitney rank sum test, Spearman rank correlation, and linear regression were used to compare median CTX values within and between groups from early to late pregnancy and associations with maternal bone outcomes. In total, 372 women had CTX and 25(OH)D measured in early and late pregnancy. CTX at 14 and 34 weeks of gestation was correlated in both the placebo (r = 0.31) and cholecalciferol (r = 0.45) groups (p < 0.0001). Median CTX increased from 14 to 34 weeks of gestation in both groups [n = 372 total; placebo (n = 188): from 223.6-449.7  $\mu\text{g}/\text{mmol}$  creatinine; cholecalciferol (n = 184): from 222.3-419.3  $\mu\text{g}/\text{mmol}$  creatinine; p = 0.03 for placebo compared with cholecalciferol difference in CTX at 34 weeks of gestation]. The conditional mean  $\pm$ SD increase in CTX [z score (SD)] from early to late pregnancy was greater in the placebo group (n = 188) than in the cholecalciferol group (n = 184) (placebo: 0.16  $\pm$ 0.92; cholecalciferol: -0.16  $\pm$ 1.06; p difference < 0.01). Higher CTX at 34 weeks of gestation was associated, similarly in both groups, with lower maternal total hip and lumbar spine bone mineral content and BMD (lumbar spine BMD:  $\beta$  = -0.02 g  $\text{cm}^{-2}$  SD-1 increase in CTX; 95% CI, -0.027 to -0.002 g  $\text{cm}^{-2}$  SD-1; p = 0.02; n = 283). The authors concluded that a bone resorption marker, maternal urinary CTX, rises throughout pregnancy, although to a lesser degree with gestational cholecalciferol supplementation, and is inversely associated with maternal bone mass postpartum. Limitations include the possibility that some participants were taking vitamin D in addition to the study drug. In addition, the use of CTX as a marker of bone resorption should also be recognized, including its circadian rhythm and relation to food intake (although early-morning, second-void urine was used to minimize this variation). Although the differences in CTX between groups and associations with bone indices are biologically plausible and consistent with existing medical literature, they should be recognized as post hoc and require replication.

Migliorini et al. (2021a) performed a systematic review of RCTs to investigate the use of BMTs in predicting clinical outcomes in postmenopausal osteoporosis. A total of 35 RCTs and 36,706 individuals were included. Data concerning bone alkaline phosphatase (bALP), serum cross-linked C-telopeptides of type I collagen, and urinary cross-linked N-telopeptides of type I collagen (NTx) were extracted at baseline and the last follow-up. The outcomes of interest were to assess the association between biomarkers and characteristics of the individuals, bone mass density, and adverse events at the last follow-up. No time constraints were set for the database search. Study generalities (author, year, journal,

duration of follow-up, daily calcium and vitamin D supplementation, and treatment) and baseline demographic information for the individuals were collected: number of samples, mean age, BMI, mean BMD (overall, spine, hip, and femur neck), t score (spine, hip, and femur), and number of previous vertebral and nonvertebral fragility fractures. Data concerning the following end points were collected at the last follow-up: mean BMD (overall, spine, hip, and femur neck); rate of vertebral, nonvertebral, femoral, and hip fragility fractures; and body height. Data concerning the following adverse events at the last follow-up were collected: overall adverse events, serious adverse events and those leading to study discontinuation, gastrointestinal events, musculoskeletal events, rate of osteonecrosis, and mortality. Results revealed that values of NTx at baseline were associated with a greater rate of adverse events at the last follow-up ( $p = 0.02$ ). Greater values of CTX at baseline were associated with a greater rate of adverse events leading to discontinuation ( $p = 0.04$ ), gastrointestinal adverse events ( $p = 0.0001$ ), musculoskeletal adverse events ( $p = 0.04$ ), and mortality ( $p = 0.04$ ). Greater values of PINP at baseline were associated with greater rates of gastrointestinal adverse events ( $p = 0.02$ ) at the last follow-up. The authors concluded that their systematic review supports the adoption of BMTs during pharmacological therapy in individuals with postmenopausal osteoporosis; however, further studies are needed to validate the use of BMTs in clinical practice. Limitations include a high risk of bias due to data based on a large population. The available literature does not include data regarding the therapeutic role of these BMTs nor did the studies evaluate BMTs as primary outcomes. In addition, future studies are needed to standardize measurement methods of BMTs.

A systematic review and meta-analysis by Migliorini et al. (2021b) were performed to evaluate the role of BTMs as therapy monitoring for postmenopausal individuals with osteoporosis. The authors reviewed RCTs comparing two or more pharmacological treatments for postmenopausal osteoporosis. Only studies that reported the value of bALP, PINP, serum cross-linked CTX, and NTx at the last follow-up were included. A multivariate analysis was performed to assess associations between these biomarkers and clinical outcomes and the rate of adverse events in postmenopausal individuals with osteoporosis. A multiple linear model regression analysis through the Pearson product-moment correlation coefficient was used. The study included a total of 16 RCTs (14,446 individuals). The median age was 67 years, and the median BMI was 25.4 kg/m<sup>2</sup>. The median vertebral BMD was 0.82, the hip BMD was 0.79, and the femur BMD was 0.64 g/cm<sup>2</sup>. The analysis of variance test found optimal within-group variance concerning mean age, BMI, and BMD. Greater bALP was associated with lower femoral BMD ( $p = 0.01$ ). Greater NTx was associated with a greater number of nonvertebral fractures ( $p = 0.02$ ). Greater NTx was associated with a greater rate of therapy discontinuation ( $p = 0.04$ ). No other statistically significant associations were detected. The authors concluded that their analysis supports the adoption of BTMs in therapy monitoring of individuals with osteoporosis. Limitations include an enhanced risk of bias due to analyses being performed regardless of drug type and administration. The findings of this study need to be validated by well-designed studies, and further investigation is needed before the clinical usefulness of this procedure is proven.

Tian et al. (2019) completed a meta-analysis study to investigate whether CTX and PINP BTMs are associated with fracture. Nine prospective cohort studies, including 11,572 individuals, from inception to August 22, 2018, and then updated on October 14, 2018, were included in the meta-analysis. The average follow-up time ranged from 2.0 to 7.13 years. The primary outcome of interest was the crude and adjusted associations of BTMs (i.e., s-PINP or s-CTX) with incidence of fracture, expressed by hazard ratio for fracture per SD difference (the gradient of risk) and 95% CI. The crude and adjusted effect size between PINP and fracture were extracted from two and five studies, respectively. PINP was not associated with fracture incidence without adjusting covariates (crude GR, 1.03; 95% CI, 0.91-1.17). After adjusting for potential confounders, PINP demonstrated a significant positive association with fracture (adjusted GR, 1.28; 95% CI, 1.15-1.42). In the subgroup analysis of studies after adjusting covariates, significant associations were observed in women. Both the crude (1.16; 95% CI, 1.04-1.20) and adjusted GR (1.20; 95% CI, 1.05-1.37) showed positive relationships between CTX and fracture, which were extracted from four and six studies, separately. The sensitivity analysis confirmed the stability of the results. In the subgroup analysis of studies after adjusting covariates, significant associations in the subgroups of elderly individuals, female individuals, and individuals with hip fracture were observed. The authors concluded that BTMs hold promise as an independent predictor for fracture. Limitations include varying metrics, false positives related to several fracture end points, and a variety of settings for adjustment among the studies. The findings of this study need to be validated by well-designed studies. Further investigation is needed before the clinical usefulness of this procedure is proven.

A systematic review was performed by Lorentzon et al. (2019) to evaluate an algorithm for the use of BMTs in the diagnosis, assessment, and follow-up of treatment for osteoporosis. The aim of this study is to provide guidance, based on the opinion of the authors, to clinicians on how to use BTMs in evaluating individuals, predicting fracture risk, and monitoring treatment effect and adherence to oral bisphosphonates in postmenopausal osteoporosis. An international working group was gathered to develop recommendations for the use of BTMs in the diagnosis and treatment of osteoporosis during a 1-day in-person meeting in Geneva on February 5, 2019, hosted by the Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases. The International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine

recommend that the bone formation marker PINP and resorption marker  $\beta$ -CTX be used as reference markers and measured in serum using standardized assays. These markers were chosen based on several criteria, including adequate characterization of the marker, specificity to bone, performance in clinical studies, biological and analytical variability, wide availability, potential for standardization of methods, sample handling, stability, and medium of measurement (serum vs urine). The use of BTMs has been extensive in clinical trials, prospective cohort studies, and case-control studies and at many clinics included in standard patient evaluation for many years; their value in clinical practice is not entirely clear. Limitations include challenges relating to large preanalytical (diurnal variations, feeding, age, gender, menopausal status, etc.) and analytical variations. The use of a multitude of markers in different clinical scenarios has impaired the interpretation of their value and makes recommendations for their use in the individual more difficult. The authors concluded that BTMs cannot be used to diagnose osteoporosis but can be of value in the evaluation of individuals and can improve the ability to detect some causes of secondary osteoporosis.

An ECRI (2018) Health Technology Assessment was conducted on BTMs in age-related osteoporosis. The assessment included one systematic review, one RCT, and six case series. ECRI concluded that there is insufficient evidence to determine whether BTMs are useful in diagnosing osteoporosis or monitoring response to osteoporosis treatment because the studies reported mixed results and are at risk of bias. The evidence was also insufficient to determine whether BTMs can determine fracture risk. Additional research is needed to determine whether BTMs are appropriate for monitoring osteoporosis treatment response.

Crandall et al. (2018) performed a prospective, case-control study that included 800 participants (400 cases with hip fracture and 400 matched controls) to determine the associations of serum CTX and serum PINP with hip fracture risk. This study was nested in the Women's Health Initiative observational study, which enrolled participants across 40 US clinical centers. Ages of participants were 50 to 79 years, with an absence of serious medical conditions. Information on the participants with hip fractures was collected by annual self-questionnaires but confirmed by medical record review. Participants in the control and case groups provided 12-hour fasting morning serum samples for CTX and PINP. The author analysis identified that serum CTX and PINP were not significantly associated with the risk of hip fracture. Limitations of the study include the inability to adjust for BMD since this study was part of the larger Women's Health Initiative study, and no sample stability data were available regarding the stored serum samples. However, the study has several strengths, including the prospective design, long-term follow-up, medical record verification on fracture information, and fasting serum samples. In summary, the authors concluded that the results do not support the utility of serum CTX level or PINP level to predict hip fracture risk in women in this age group.

## **Clinical Practice Guidelines**

### ***American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)***

In their 2016 clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis, the AACE and ACE remark that BTMs can provide a dynamic assessment of skeletal activity and are useful modalities for skeletal assessment. Although they alone cannot be used to diagnose osteoporosis, elevated BTM levels can predict more rapid rates of bone loss and are associated with increased fracture risk, independent of BMD (grade A; best evidence level 1). However, their use in clinical practice is limited by high in vivo and assay variability (e.g., urinary resorption markers), poor predictive ability in individual patients, and lack of evidence-based thresholds for clinical decision-making. Use of BTMs for assessing patient adherence and therapy efficacy should be considered. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction; significant increases indicate good response to anabolic therapy (grade B; best evidence level 1, adjusted down due to limited evidence) (Camacho et al., 2016). An updated review of literature performed by Camacho et al. (2020) reaffirmed that there is no new evidence that conflicts with the previous recommendations published in the original version of the guideline.

### ***Bone Health and Osteoporosis Foundation (BHOFF)***

In a 2022 consensus statement, the BHOFF states that with measurable benchmarks such as BMD, fracture incidence, and biochemical markers of bone turnover, the treat-to-target strategy of outcomes-focused therapy, monitoring, and reassessment can be applied to the management of osteoporosis. In addition, measurements of biochemical BTMs can play a role in assessing fracture risk in appropriate patients. The BHOFF states that BTMs may:

- Predict the rapidity of bone loss in untreated postmenopausal women
- Predict the extent of fracture risk reduction when repeated after 3 to 6 months of treatment with US Food and Drug Administration–approved therapies
- Predict the magnitude of BMD increases with US Food and Drug Administration–approved therapies
- Characterize patient adherence and persistence with osteoporosis therapy using a serum CTX for an antiresorptive medication and P1NP for an anabolic therapy (least significant change is approximately a 40% reduction in CTX)

- Potentially be used during a bisphosphonate holiday to suggest when medication should be restarted, although more data is needed to support this recommendation (LeBoff et al., 2022)

### ***Endocrine Society (ES)***

The 2020 Clinical Practice Guideline update on Pharmacological Management of Osteoporosis in Postmenopausal Women states the following:

- In postmenopausal women with a low BMD, who are at high risk of fractures and are being treated for osteoporosis, it is suggested to monitor the BMD by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment.
- Technical remark: Monitoring BTMs (serum C-terminal cross-linking telopeptide for antiresorptive therapy or procollagen type N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy (Eastell et al., 2019; updated Shoback et al., 2020).

The 2012 Clinical Practice Guideline on Osteoporosis in Men recommends the following:

- Clinicians consider measuring a BTM at 3 to 6 months after initiation of treatment using a bone resorption marker (such as serum CTX or serum or urine NTx) for antiresorptive therapy and a bone formation marker (such as serum PINP) for anabolic therapy (Watts et al., 2012).

### ***European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)/International Osteoporosis Foundation (IOF)/International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)***

In a 2025 consensus paper by ESCEO, IOF and IFCC the following recommendations were proposed on the role of BTMs and newer markers in the diagnosis and management of osteoporosis and states:

- Serum PINP and plasma  $\beta$ -CTX-I are re-affirmed as reference BTMs in osteoporosis and are considered useful for monitoring anti-osteoporosis therapy
- The use of bone formation marker BALP and resorption marker TRACP5b as the reference markers for formation and resorption respectively in CKD-associated osteoporosis

The authors concluded BTMs show promise as an independent fracture predictor, but further prospective cohort studies are needed, including in CKD associated osteoporosis, to examine their interaction with established risk factors in order for possible inclusion in fracture risk assessment tools. In addition, studies relating to BTM changes to fracture risk reduction should be performed in order to provide further guidance on optimal treatment targets for BTM in monitoring therapy efficacy and managing cessation of treatment and drug holiday (Bhattoa, 2025).

### ***International Society for Clinical Densitometry (ISCD)***

The 2023 ISCD position on serial BMD measurements recommends serial BMD testing, in combination with clinical assessment of fracture risk, BTMs, and other factors, including height loss and trabecular bone score, can be used to determine whether treatment should be initiated in untreated patients, according to locally applicable guidelines (Kendler et al., 2019; updated Shepherd, 2023).

### ***International Society for Clinical Densitometry (ISCD)/International Osteoporosis Foundation (IOF)***

The 2023 ISCD/IOF position for FRAX clinical regarding biochemical markers states that the evidence that BTMs predict fracture risk independent of BMD is inconclusive. Therefore, BTMs are not included as risk factors in FRAX (McCloskey et al., 2011; updated Shepherd, 2023).

### ***North American Menopause Society (NAMS)***

A 2021 NAMS position statement on the management of osteoporosis in postmenopausal women states that BTMs cannot diagnose osteoporosis and have varying ability to predict fracture risk in clinical trials. The routine use of BMTs in clinical practice is not recommended.

### ***Osteoporosis Canada (OC)***

An updated 2023 OC clinical practice guideline for management of osteoporosis and fracture prevention in Canada suggests against monitoring using BTMs for fracture prevention or for deciding on resumption of therapy in people who have stopped bisphosphonates (drug holiday). Conditional recommendation; very low-certainty evidence (Morin et al., 2023).

A 2002 OSC clinical practice guideline for the diagnosis and management of osteoporosis in Canada states that BTMs should not yet be used for routine clinical management. Additional studies are needed to confirm their use in individual patients (Brown and Josse, 2002).

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA regulates commercially marketed tests and test systems such as bone markers and categorizes these test systems into one of three Clinical Laboratory Improvement Act (CLIA) of 1988 regulatory categories (e.g., waived, moderate, high) based on their potential risk to public health. Commercially marketed tests that have received 510(k) marketing clearance can be accessed through the 510(k) database (search by manufacturer or test system name) or through the CLIA database (search by manufacturer, test system, or analyte name). Laboratories that use their own tests but do not market the kits to others are subject to the standards of the CLIA but not to FDA marketing regulations.

Information was not identified regarding FDA-approved osteoporosis treatments and the use of biochemical markers in the diagnosis of osteoporosis or in the selection, dosing, or administration of these drugs. In addition, the FDA consumer-focused website publication on osteoporosis does not include biochemical markers in its list of diagnostic tests. For additional information, refer to: <https://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118551.htm>. (Accessed September 11, 2024)

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## Policy History/Revision Information

Date	Summary of Changes
04/01/2026	<ul style="list-style-type: none"> <li>Retired policy; Louisiana plan membership disenrolled on Apr. 1, 2026</li> </ul>

Date	Summary of Changes
03/01/2026	<p data-bbox="337 132 662 165"><b>Supporting Information</b></p> <ul data-bbox="337 165 1511 254" style="list-style-type: none"> <li data-bbox="337 165 1511 222">• Updated <i>Description of Services</i>, <i>Clinical Evidence</i>, <i>FDA</i>, and <i>References</i> sections to reflect the most current information</li> <li data-bbox="337 222 1511 254">• Archived previous policy version CS021LA.M</li> </ul>

## Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.