Collagen Crosslinks and Biochemical Markers of Bone Turnover

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Instructions for Use

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Commercial Policy
• Collagen Crosslinks and Biochemical Markers of Bone Turnover

Application

This Medical Policy does not apply to the states listed below; refer to the applicable policy/guideline:

State	Policy/Guideline
Indiana	None
Kentucky	Collagen Crosslinks and Biochemical Markers of Bone Turnover (for Kentucky Only)
Louisiana	Collagen Crosslinks and Biochemical Markers of Bone Turnover (for Louisiana Only)
Nebraska	Collagen Crosslinks and Biochemical Markers of Bone Turnover (for Nebraska Only)
New Jersey	Collagen Crosslinks and Biochemical Markers of Bone Turnover (for New Jersey Only)
North Carolina	Collagen Crosslinks and Biochemical Markers of Bone Turnover (for North Carolina Only)
Pennsylvania	Collagen Crosslinks and Biochemical Markers of Bone Turnover (for Pennsylvania Only)
Tennessee	Collagen Crosslinks and Biochemical Markers of Bone Turnover (for Tennessee Only)

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 (HPLC) 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 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 (NTx) (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 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 patient. While these are frequently used in research studies, the use of biochemical markers in clinical practice is controversial because of the complexity of interpreting the values for individual patients related to the intricacies inherent in bone metabolism, and the lack of standardization, which has led to unacceptable levels of variation between processing laboratories.

Clinical Evidence

The utility of collagen crosslinks and bone turnover biomarkers tests is disputed, but their use is emerging for the management of osteoporosis. While they may help add to the prediction of a risk for fracture, these tests lack standardization. There is insufficient clinical evidence to consider them useful in clinical practice and proven to improve patient care; therefore, additional studies and clinical trials are needed to demonstrate their efficacy.

A randomized controlled trial was completed by Ma et al. (2021) to evaluate the effect of bone turnover marker (BTM) monitoring to guide the treatment of osteoporosis in postmenopausal females undergoing total knee arthroplasty (TKA) from April 2017 to December 2018. The study included a total of 64 patients, divided into two groups: monitoring group (n = 32) and a control group (n = 32). The patients were given oral medication (alendronate, calcitriol, and calcium), and followed for one year. In the monitoring group, serum BTMs (C-telopeptide of type I collagen (CTX-I), N-terminal propeptide of type I procollagen (PINP), and 25(OH)D were assessed preoperatively and repeated postoperatively; 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 (MTPM) of the tibial component, bone mineral density (BMD), visual analog scale (VAS) score, range of motion, and Oxford Knee Score (OKS) 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 MTPM values at 6 m and 12 m in the monitoring group were lower than those in the control group, and the BMD at 12 m in the monitoring group was significantly higher than that in the control group. Patients in the monitoring group had lower VAS scores at 6 m and higher OKS scores at 6 m and 12 m 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 outcome in postmenopausal females with osteoporosis undergoing primary TKA. Limitations include small sample size and short-term follow-up which did not allow for assessment of long-term outcomes. In addition, several patients in the study were non-compliant with follow-up and/or refusal to provide blood samples post-operatively. Further research is needed to determine the clinical relevance of these findings.

A sub-analysis of a randomized controlled trial was performed by Curtis et al. (2021) to evaluate markers of maternal bone resorption, urinary C-terminal telopeptide of type I collagen (CTX), influence of gestational vitamin D supplementation, and

associations between CTX and maternal postnatal bone indices across pregnancy. MAVIDOS (the Maternal Vitamin D Osteoporosis Study) is a randomized, double-blind, placebo-controlled trial of 1000 IU cholecalciferol/d compared with placebo from 14 weeks of gestation to birth. Maternal second-void urinary α- and β-CTX were measured (ELISA) at 14 and 34 weeks of gestation; DXA was performed within 2 weeks postpartum. The Mann–Whitney Rank Sum test, Spearman's 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-hydroxyvitamin D [25(OH)D] measured in early and late pregnancy. CTX at 14 and 34 weeks of gestation were correlated in both 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 to 449.7 μg/mmol creatinine; cholecalciferol (n = 184): from 222.3 to 419.3 μg/mmol creatinine; P = 0.03 for placebo compared with cholecalciferol difference in CTX at 34 weeks of gestation]. The conditional mean ±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 ±0.92; cholecalciferol: −0.16 ±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 bone mineral density (BMD) (e.g., lumbar spine BMD: β = −0.02 g · cm−2 · SD−1 increase in CTX; 95% CI: −0.027, −0.002 g · cm−2 · SD−1; P = 0.02, n = 283). The authors concluded that bone resorption marker, maternal urinary CTX, rises through 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 with 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 randomized controlled trials (RCTs) to investigate the use of biochemical markers of bone turnover (BMTs) in predicting clinical outcomes in post-menopausal osteoporosis. A total of 35 RCTs and 36,706 patients were included. Data concerning bone alkaline phosphatase (bALP), procollagen type I N propeptide (PINP), serum cross-linked C-telopeptides of type I collagen (bCTx), and urinary cross-linked N-telopeptides of type I collagen (NTx) were extracted at baseline and last follow-up. The outcomes of interest were to assess the association between biomarkers and patient characteristics, 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 the follow-up, daily calcium and vitamin D supplementation, treatment) and patient baseline demographic information were collected: number of samples, mean age, mean bone mass index (BMI), mean BMD (overall, spine, hip, femur neck), t score (spine, hip, femur), and number of previous vertebral and non-vertebral fragility fractures. Data concerning the following endpoints were collected at the last follow-up: mean BMD (overall, spine, hip, femur neck), rate of vertebral, non-vertebral, femoral, 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 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 patients with post-menopausal osteoporosis, however, further studies are needed to validate the use of BMTs in clinical practice. Limitations include a high risk for 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 biochemical markers of bone turnover (BMTs) as therapy monitoring for post-menopausal osteoporotic patients. The authors reviewed randomized clinical trials (RCTs) comparing two or more pharmacological treatments for post-menopausal osteoporosis were accessed. Only studies that reported the value of bALP, PINP, bCTx, and NTx at last follow-up was included. A multivariate analysis was performed to assess associations between these biomarkers and clinical outcomes and rate of adverse events in patients with postmenopausal 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 patients).The median age was 67 years, and the median BMI 25.4 kg/m2. The median vertebral BMD was 0.82, hip BMD 0.79, and femur BMD 0.64 g/cm2. The ANOVA test found optimal within-group variance concerning mean age, body mass index, and BMD. Greater bALP was associated with lower femoral BMD (P = 0.01). Greater NTx was associated with a greater number of non-vertebral fractures (P = 0.02). Greater NTx

was associated with 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 osteoporotic patients. Limitations include and 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 clinical usefulness of this procedure is proven.

A meta-analysis was completed by Tian et al. (2019) to investigate whether C-terminal telopeptide of type I collagen (CTX) and procollagen type I amino terminal propeptide (PINP) bone turnover biomarkers (BTMs) are associated with fracture. Nine prospective-cohort studies including 11,572 patients, 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 HR for fracture per SD difference (the GR) and 95% confidence interval (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, there were significant associations in women. Both the crude (1.16, 95% CI, 1.04-1.20) and adjusted GR (1.20, 95% CI, 1.05-1.37) shown 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, there were significant associations in the subgroups of elderly, female, and hip fracture patients. The authors conclude that BTMs hold promise as an independent predictor for fracture. Limitations include varying metrics, false positives related to several fracture endpoints 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 clinical usefulness of this procedure is proven.

A systematic review performed by Lorentzon et al. (2019) to evaluate an algorithm for the use of biochemical markers (BTMs) of bone turnover 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 experts of the authors, to clinicians on how to use bone turnover markers in patient evaluation, in fracture risk prediction and in monitoring treatment effect and adherence to oral bisphosphonates in postmenopausal osteoporosis. An international working group was gathered to develop recommendations for the use of bone turnover markers 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 European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO). The IOF and International Federation of Clinical Chemistry and Laboratory Medicine recommend that the bone formation marker PINP and resorption marker ßCTX-I 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 bone turnover markers has been extensive in clinical trials, prospective cohort studies, 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 pre-analytical (diurnal variations, feeding, age, gender, menopausal status, etc.) and analytical variations. The use of a multitude of markers in different clinical scenarios have impaired the interpretation of their value and makes recommendations for their use in the individual patient more difficult. The authors concluded that 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.

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 C-terminal telopeptide of type one collagen (CTX) and serum procollagen type I amino terminal propetitide (PINP) with hip fracture risk. This study was nested in the Women's Health Initiative (WHI) Observational Study, which enrolled participants across 40 U.S. clinical centers. Ages for participants were 50-79 years with an absence of serious medical conditions. Information for 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 the serum CTX and PINP was not significantly associated with risk of hip fracture. Limitations of the study included the inability to adjust for bone mineral density since this study was part of the larger WHI study and no sample stability data regarding the stored serum samples. However, the study had several strengths including prospective design, long term follow up, medical record follow for fracture information

and fasting serum samples. In summary, the authors concluded the results did not support the utility of serum CTX level or PINP level to predict hip fracture risk in women in this age group.

Jørgensen et al. (2017) investigated the associations between bone turnover markers, bone mineral density (BMD), and prevalent fragility fracture in a cohort of kidney transplantation candidates. Volumetric BMD of spine and hip was measured by quantitative computed tomography. Parathyroid hormone (PTH), bone-specific alkaline phosphatase, procollagen type-1 N-terminal propeptide, tartrate resistant alkaline phosphatase, and C- and N-terminal telopeptides of type 1 collagen were analyzed from fasting morning blood samples. Fragility fractures included prevalent vertebral fractures and previous low-trauma clinical fractures. The fracture prevalence was 18% in 157 adult kidney transplant candidates. Fractured patients had reduced BMD and Z-score at both spine and hip. Levels of bone turnover markers were significantly higher in patients on maintenance dialysis than in pre-dialysis patients; but did not differ between patients with and without fracture. There were strong, positive correlations between PTH and all bone turnover markers. PTH was negatively associated with Z-score at lumbar spine and total hip; in contrast, bone turnover markers were only negatively associated with total hip Z-score. The results showed that bone turnover markers were negatively associated with bone density, but not associated with prevalent fracture in kidney transplantation candidates. The role of bone turnover markers in assessing bone fragility in CKD requires further investigation.

A systematic review published in 2012 by Biver and colleagues reviewed the literature on bone turnover markers for diagnosing osteoporosis and predicting fracture risk. To be included in the review, studies needed to report at least one bone turnover marker and report either BMD or fracture assessment. In post-menopausal women, the markers that have been studied the most and also have the strongest negative correlations with BMD are alkaline phosphatase (ALP), osteocalcin (OC), type 1 cross-linked C-telopeptide (CTx), and type 1 cross-linked N-telopeptide (NTx). The investigators addressed the issue of the potential association between bone turnover markers and prevalent asymptomatic vertebral fractures. A pooled analysis was conducted only for the marker osteocalcin (OC). When findings from 3 studies were pooled, there was not a statistically significant mean difference in OC levels in patients with and without vertebral fractures. The authors also reported that bone turnover markers were not able to reliably distinguish primary osteoporosis from secondary causes. There was a high degree of heterogeneity among the published studies included in this review. According to these data, the clinical usefulness of bone turnover markers for diagnosing osteoporosis is low due to patient variability and other factors that can influence bone turnover marker levels.

Trento et al. (2009, included in the Biver systematic review cited above) investigated the clinical role of the bone turnover markers type I collagen C telopeptide (CTX), osteocalcin (OC) and bone-specific alkaline phosphatase (BAP) in the assessment of bone status in 200 women with postmenopausal osteoporosis. Serum bone turnover markers were measured at the initial visit and correlated with spine and femur bone mineral density (BMD), determined on dual-energy X-ray absorptiometry. No correlation was found between serum levels of OC and BAP and vertebral or femur BMD when analyzed against biochemical markers of bone turnover and age, age at menopause, body mass index (BMI) and BMD. S-CTX levels were higher in women with osteoporosis than in women with normal or moderately low (osteopenic) values of BMD. The sensitivity and specificity versus spine BMD were 73.9% and 41.6% for s-CTX, 40.4% and 80.6% for BAP, and 68.3% and 39% for OC, respectively. The sensitivity and specificity versus femur BMD were 76.9% and 40.4% for s-CTX, 23.8% and 88.3% for BAP, and 80.4% and 53.3% for OC, respectively. The authors concluded that determination of s-CTX, BAP and OC is of limited clinical value in the initial evaluation of bone status in menopausal women.

Lukaszkiewicz et al. (2008) evaluated the correlation between bone resorption and bone formation markers to assess bone turnover rate and qualify an individual postmenopausal woman as a possible elevated bone turnover (EBT) subject. A total of 320 postmenopausal women were enrolled at seven clinical sites in this cross-sectional observational study. The group was a random sample of the population. BMD measurements of the lumbar spine, total hip, trochanter, and femoral neck regions were performed. Bone resorption and formation rates were evaluated by serum levels of C-terminal telopeptide of type I collagen (CTX) and osteocalcin (OC), respectively. Using logistic regression to correlate the concentrations of CTX and OC it was possible not only to distinguish the EBT subgroup, but also to construct a simple nomogram for easy classification of individual patients as possible EBT subjects. EBT patients showed generally decreased BMD values and increased bone formation and resorption rates. The investigators concluded that evaluation of both CTX and OC levels enables a more proper indication for EBT.

An observational study that included 432 Japanese elderly women who were not receiving any drug treatment for osteoporosis were followed for 5.2 +/- 3.3 years. Vertebral fractures and bone mineral density were assessed at baseline and then at 1- to 2-year intervals or at indication of any symptom. Two types of collagen metabolites were measured at baseline: urinary N-terminal

telopeptide of type I collagen (NTX), a marker of pyridinium cross-link, and urinary pentosidine, a nonenzymatic collagen cross-link produced by AGEs. A total of 97 incident vertebral fractures on 72 subjects were observed. Simple regression analysis using Cox's hazards model showed that log-transformed urinary NTX and pentosidine are significant risk factors for time-dependent incidence of vertebral fractures, in addition to the traditional risk factors (age, lumbar bone mineral density, and number of prevalent vertebral fractures). However, urinary excretion of pentosidine was a significant predictor of incident vertebral fracture after adjustment for other traditional risk factors. The authors concluded that their data suggest that AGE-related collagen cross-link is a novel risk for vertebral fracture (Shiraki et al., 2008). Based on these findings alone, it is however unclear whether the use of these biomarkers improve patients'' outcomes.

Several nonrandomized controlled trials also discussed the potential value of bone turnover markers (Meier, 2005; Worsfold, 2004; Garnero, 2000; Iki, 2006). However, no outcomes studies were found in which patient management was changed by the results of bone turnover markers.

Parviainen et al. (1999) studied the clinical usefulness of urinary bone resorption markers in postmenopausal women with symptomatic osteoporosis in a randomized double-blind placebo controlled study in which patients were daily treated for 24 months either with a hormone analogue plus 800 mg calcium (n = 14), or with placebo plus 800 mg calcium (n = 19). All resorption markers decreased for both groups during the 2 years the study was conducted. After 2 years there was, however, a significant increase in bone density both in the spine and in the femoral neck in the women with hormone treatment. In the control group a significant increase (P = 0.0012) in the spine, whereas a non-significant decrease in the femoral neck was observed. The investigators concluded that measurement of urinary cross-linked peptides derived from Type I collagen (NTx and DPD) might be a useful biochemical method of observing the positive clinical effect (i.e., reduction in bone resorption) following hormone replacement therapy in postmenopausal fracture patients.

Marcus et al. (1999) assessed the associations of eight bone turnover markers (BTMs) with baseline and 1-year percentage changes in lumbar spine and hip bone mineral density (BMD) of 293 postmenopausal women undergoing treatment with hormone replacement therapy (HRT) (n = 293) or placebo (n = 54). In 239 women assigned to treatment with estrogen alone or with estrogen plus progestins (active treatment), mean percentage changes for all markers decreased significantly and remained below baseline values through 3 years of study, whereas mean percentage changes for 54 women assigned to the placebo group showed no significant change from baseline in any marker. The investigators concluded that BTMs are not a surrogate for BMD to identify women with low bone mass and that they offer little useful information for predicting BMD changes for individual untreated or HRT-treated postmenopausal women.

A position statement from the National Bone Health Alliance Working Group (2014) supports the continued use of bone mineral density (BMD) testing and FRAX for diagnosis of osteoporosis; there is no recommendation for biochemical marker use.

The National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases National Resource Center (2015) does not address bone remodeling, or biomarkers in relation to screening for osteoporosis and fracture risk.

The U.S. Preventive Services Task Force (USPSTF) 2018 final recommendation on screening for osteoporosis to prevent fractures does not include biochemical marker assessment of bone turnover as a diagnostic tool.

The National Institute for Health and Care Excellence (NICE) (2017) does not include biochemical markers in their recommendation for osteoporosis and assessing the risk of fragility fracture.

The IOF and the National Osteoporosis Foundation (NOF) created a consensus paper on the role of biochemical markers of bone turnover in the management of metabolic bone diseases to address the controversial nature of the topic. They conclude that in patients of both genders suffering from osteoporosis, bone turnover markers (BTMs) alone cannot provide a substantial contribution to the diagnosis of the disease. In addition, particularly in elderly patients, comorbidities or co-prescriptions may significantly influence the level of BTMs, making their interpretation more convoluted. Therefore, their use as diagnostic tools in secondary osteoporosis, particularly in glucocorticoid-induced osteoporosis, remains in the authors' opinion highly equivocal. Finally, the practical use of BTMs in clinical practice does not clearly appear. Eventually, with the new anti-osteoporosis chemical entities that are currently developed for the management of osteoporosis, BTMs may be difficult to interpret and to follow, as they may substantially change over time, reflecting the complex mechanism of action of these new therapies. BTMs remain today one of the less invasive approaches to better understand the dynamics of bone remodeling and, in some cases, to monitor the activity of medicines that interfere either with bone formation or bone resorption (Cavalier et al., 2016).

Clinical Practice Guidelines

American Academy of Family Physicians (AAFP)

The AAFP 2015 guideline on diagnosis and management of osteoporosis does not address biochemical markers for the diagnosis and management of osteoporosis (Jeremiah et al. 2015).

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 (Camacho et al., 2016) remark that bone turnover markers (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 bone marrow density (grade B; best evidence level 1, downgraded based on expert consensus). Their use in clinical practice, however, 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. Consider using BTMs for assessing patient compliance and therapy efficacy. 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; downgraded based on expert consensus). 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.

American College of Obstetricians and Gynecologists (ACOG)

An ACOG practice bulletin addresses the use of biochemical markers to predict bone turnover in osteoporosis. The guideline states that bone turnover markers cannot be used to diagnose osteoporosis, and the usefulness of markers as an incentive for adherence has been questioned (ACOG, 2012; reaffirmed 2016).

The International Society for Clinical Densitometry (ISCD)

An updated review (Akid & Doberman, 2021) of ISCD clinical practice guidelines (2019) for the surveillance and management of osteoporotic patients treated with oral or intravenous therapy suggest a follow-up dual-energy x-ray absorptiometry (DEXA) scan of hip and spine after 2 years of initiating therapy for osteoporosis, with less frequent monitoring thereafter. There is no consensus on the optimal frequency of monitoring. In addition, bone turn-over markers such as fasting urinary N-telopeptide or serum carboxy-terminal collagen crosslinks are not recommended for measurement, except for special circumstances where malabsorption of antiresorptive medications may be an issue.

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 to one of three Clinical Laboratory Improvement Act (CLIA) of 1988 regulatory categories (i.e., waived, moderate, or 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 Clinical Laboratory Improvement Act (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, see: https://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118551.htm. (Accessed February 14, 2022)

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Policy History/Revision Information

Date	Summary of Changes
06/01/2022	Application *Mississippi* • Updated language to indicate this Medical Policy applies to the state of Mississippi (retired state-specific policy version) Supporting Information • Archived previous policy version CS021.K

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, please 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.

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