Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

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

Description/Background

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

BONE TURNOVER

After cessation of growth, bone is in a constant state of remodeling (or turnover), with initial absorption of bone by osteoclasts followed by deposition of new bone matrix by osteoblasts. This constant bone turnover is critical to the overall health of the bone, by repairing microfractures and remodeling the bony architecture in response to stress. Normally, the action of osteoclasts and osteoblasts is balanced, but bone loss occurs if the 2 processes become uncoupled. Bone turnover markers can be categorized as bone formation markers or bone resorption markers and can be identified in serum and/or urine. Table 1 summarizes the various bone-turnover markers.[3]

Table 1. Bone Turnover Markers

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

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

Bone Density

There is interest in the use of bone turnover markers to evaluate age-related osteoporosis, a disease characterized by slow, prolonged bone loss, resulting in an increased risk of fractures at the hip, spine, or wrist. Currently, fracture risk is primarily based on measurements of bone mineral density (BMD) in conjunction with other genetic and environmental factors, such as family history of osteoporosis, history of smoking, and weight. It is thought that the level of bone turnover markers may also predict fracture risk, possibly through a different mechanism than that associated with BMD.

In addition, bone turnover markers might provide a more immediate assessment of treatment response and predict change in BMD in response to treatment. Treatment-related changes in BMD occur very slowly. This fact, coupled with the precision of BMD technologies, suggested that clinically significant changes in BMD could not be reliably detected until at least 2 years. In contrast, changes in bone turnover markers could be anticipated after 3 months of therapy.

Bone turnover markers have been researched in diseases associated with markedly high levels of bone turnover, such as Paget's disease, primary hyperparathyroidism, and renal osteodystrophy.

Regulatory Status

Several tests for bone turnover markers have been cleared by the U.S. Food and Drug Administration (FDA) using the 510(k) process. Examples are listed in Table 2. FDA product codes: NEO,JMM, CIN.

Table 2. Approved Tests for Bone Turnover Markers

Test	Manufacturer	Year	Indication
Pyrilinks®	Metra Biosystems	1995	Collagen type 1 cross-link, pyridinium
Osteomark®	Ostex International	1996	Cross-linked N-telopeptides of type 1 collagen
Serum CrossLaps® ELISA	Immunodiagnostic Systems	1999	Hydroxyproline
Ostase®	Beckman Coulter	2000	Bone-specific alkaline phosphatase
N-MID® Osteocalcin One-Step ELISA	Osteometer BioTech	2001	Osteocalcin
Elecsys® N-MID Osteocalcin	Roche Diagnostics	2005	Osteocalcin
IDS-iSYS Ostase® BAP	Immunodiagnostic Systems	2020	Bone-specific alkaline phosphatase

ELISA: enzyme-linked immunosorbent assay; FDA: U.S. Food and Drug Administration.

Medical Policy Statement

The safety and effectiveness of the measurement of alkaline phosphatase isoenzymes have been established. It is a useful option for the diagnosis and monitoring of diseases of the bone, liver and/or endocrine system.

The measurement of bone turnover markers have been established in certain situations in individuals with osteoporosis.

The measurement of bone turnover marker levels have been established. It is a useful diagnostic option for the initial diagnosis and subsequent monitoring of individuals with Paget's disease of the bone.

The measurement of bone turnover markers is considered experimental/investigational in the diagnosis and management of individuals with all other conditions associated with high rates of bone turnover, including but not limited to primary hyperparathyroidism and renal osteodystrophy. The peer reviewed medical literature has not demonstrated the clinical utility of these laboratory tests of bone turnover for improving patient clinical outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:
Measurement of bone turnover markers** for individuals with osteoporosis when one of the following is present:

- Initial evaluation of osteoporosis
- Management of individuals with osteoporosis
- Determine fracture risk prediction in individuals with osteoporosis
- In individuals treated with bisphosphonates for assessment of patient compliance with bisphosphonate therapy

Measurement of bone turnover markers** in individuals with Paget's disease of the bone when one of the following is present:

- Initial diagnosis of Paget's disease
- Subsequent monitoring and management of patients with Paget's disease of the bone.

**Bone turnover markers include (Rosen, 2018, 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

Exclusions:

- Measurement of bone turnover markers as a diagnostic test for osteoporosis
- Measurement of bone turnover markers for teriparatide treatment monitoring in individuals with osteoporosis
- Measurement of bone turnover markers in the diagnosis and management of all other conditions associated with high bone turnover including but not limited to individuals with primary hyperparathyroidism and renal osteodystrophy.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

82523 83500 83505 83937 84078
84080*

Other codes (investigational, not medically necessary, etc.):

N/A

Note: CPT code 82523 describes collagen cross-links, any method. CPT code 83937 describes osteocalcin testing.

*There is no specific CPT code for bone-specific alkaline phosphatase (ALK), but several laboratories' websites identify CPT 84080 (phosphatase, alkaline; isoenzymes) as being used for the Ostase test.

Rationale

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 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).

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." 1,069 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).

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." 1,680 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 ($P < .01$). 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).

A systematic review and meta-analysis by Al Nofal et al (2015) assessed the literature on bone turnover markers in Paget disease. Reviewers focused on the correlation between bone markers and disease activity before and after treatment with bisphosphonates. All study design types were included, and bone scintigraphy was used as the reference standard. Reviewers identified 18 studies. Seven assessed bone markers in patients with Paget disease before treatment, six considered both the pre- and posttreatment associations, and five included only the posttreatment period. Only 1 study was an RCT; the rest were prospective cohort studies. There was a moderate-to-strong correlation between several bone turnover markers (bone ALP, total ALP, PINP, NTX) and pretreatment disease activity. In a pooled analysis of available data, there was a statistically significant correlation between levels of bone turnover marker and disease activity after treatment with bisphosphonates (p=0.019). Reviewers did not address the potential impact on bone turnover measurement on patient management or health outcomes.

SUMMARY OF EVIDENCE

For individuals with osteoporosis or risk factors for age-related osteoporosis who receive a measurement of bone turnover markers to determine fracture risk, the evidence includes observational studies on the association between markers and osteoporosis and fracture risk, and systematic reviews of those studies. Relevant outcomes are test validity and morbid events. Few studies have directly addressed whether any bone turnover markers beyond bone mineral density (BMD) measurements are independent predictors of fracture risk. One meta-analysis investigated the independent role of bone turnover markers in fracture risk prediction and found a statistically significant but modest association between bone turnover markers (specifically, procollagen type 1 N-terminal propeptide and cross-linked C-telopeptide) and future fracture risk after adjusting for BMD and clinical risk factors. Other studies have suggested that bone turnover marker levels may be independently associated with osteoporosis and fracture risk in some groups. The evidence available is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are being treated for osteoporosis who receive a measurement of bone turnover markers to determine response to therapy, the evidence includes an observational study, randomized controlled trials (RCTs), and a systematic review of these RCTs. Relevant outcomes are test validity and morbid events. Although there is limited evidence on the impact of bone turnover markers on the management of osteoporosis, the use bone turnover markers may lead to management changes that are expected to improve outcomes. The evidence available is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with conditions associated with high rates of bone turnover other than age-related osteoporosis (e.g., primary hyperparathyroidism, Paget disease, renal osteodystrophy) who receive a measurement of bone turnover markers, the evidence includes observational studies on the association between markers and disease activity and systematic reviews of those studies. Relevant outcomes are test validity and morbid events. The largest amount of evidence has been published on Paget disease; a systematic review found correlations between several bone turnover markers and disease activity prior to and/or after bisphosphonate treatment. The Endocrine Society guideline recommends the “measurement of serum total alkaline phosphatase or, when warranted, a more specific marker of bone formation or bone resorption to assess the response to treatment or evolution of the disease in

untreated patients with Paget's disease of the bone." The measurement of serum osteocalcin and collagen crosslinks (serum or urine) bone turnover marker levels has been established. It is a useful diagnostic option for the initial diagnosis and subsequent monitoring of patients with Paget's disease of the bone. The use of serum osteocalcin and collagen crosslinks (serum or urine) bone turnover markers for all other conditions associated with high bone turnover, including but not limited to individuals with primary hyperparathyroidism and renal osteodystrophy, is considered experimental/investigational.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Osteoporosis Foundation (Cosman et al., 2014)

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

In 2021, the North American Menopause Society (NAMS) issued a position statement on the management of osteoporosis in postmenopausal women. Per the NAMS:

- "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. Although used by some osteoporosis specialists, the routine use of bone turnover markers in the evaluation of patients with osteoporosis is not recommended."
- "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."

The Endocrine Society
2019 guidelines from the Endocrine Society recommend that in postmenopausal women with a low BMD and at high-risk of fractures who are being treated for osteoporosis, monitoring should be conducted by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years. The Society considers measuring bone turnover markers (serum CTX for antiresorptive therapy or P1NP for bone anabolic therapy) as an alternative way of monitoring for poor response or nonadherence to therapy. The society notes that there is uncertainty over what constitutes an optimal response to treatment, but some experts suggest that a meaningful change is approximately 40% when compared from before to 3 to 6 months after starting treatment. A guideline update was published in 2020, in which the statements concerning measurement of bone turnover markers remained unchanged. The Endocrine Society also published guidelines regarding the management of Paget disease in 2014.
The guideline states:

- “We recommend measurement of serum total alkaline phosphatase or, when warranted, a more specific marker of bone formation or bone resorption to assess the response to treatment or evolution of the disease in untreated patients.”
- “In patients with monostotic disease who have a normal serum total alkaline phosphatase, we suggest that a specific marker of bone formation and bone resorption be measured, although these may still be normal. Serial radionuclide bone scans may determine the response to treatment if the markers are normal.”
- "In assessing the response to treatment: “For most patients, measurement of total ALP [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.”

International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (Vasikaran, Cooper, et al., 2011)
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 facture risk.”

American Association of Clinical Endocrinologists and the American College of Endocrinology
The 2020 guidelines from the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) gave a Grade B recommendation to consider using bone turnover markers for assessing patient compliance and therapy efficacy.
AACE/ACE reviewed evidence that markers respond quickly to therapeutic intervention, and changes in markers have been associated with bone response to therapy and fracture risk reduction.

Bone Health and Osteoporosis Foundation

In 2022, the Bone Health and Osteoporosis Foundation (formerly the National Osteoporosis Foundation) published updated guidelines on the prevention and treatment of osteoporosis to

prevent fractures. Regarding biochemical markers of bone turnover, the guidelines stated: "Biochemical bone turnover markers can play a role in assessing fracture risk in appropriate individuals."

Furthremore, biochemical markers of bone turnover may

- Predict rapidity of bone loss in untreated postmenoupausal women
- Predict extent of fracture risk reduction when repeated after 3-6 months of treatment with FDA [Food and Drug Administration]-approved therapies
- Predict magnitude of BMD [bone mineral density] increases with FDA-approved therapies
- Help determine adequacy of patient compliance and persistence with osteoporosis therapy using a serum CTX for an antiresorptive medication and P1NP for an anabolic therapy (least significant change [LSC] is approximately a 40% reduction in CTX)
- Help determine duration of 'drug holiday' and when and if medication should be restarted (Data are quite limited to support this use, but studies are underway.)

International Society for Clinical Densitometry and International Osteoporosis Foundation

In 2011, the Joint Official Positions Development Conference of the International Society for Clinical Densitometry and the IOF on the FRAX® fracture risk prediction algorithms stated:[18] "Evidence that bone turnover markers predict fracture risk independent of BMD is inconclusive. Therefore, bone turnover markers are not included as risk factors in FRAX."

In the 2019 ISCD position statement on repeating measurement of BMD when monitoring with DXA, there is a comment on bone turnover markers: "Serial BMD 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."

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:

- "The bone formation marker serum PINP [N-terminal collagen type I extension propeptide] and resorption marker serum βCTX-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 βCTX-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 βCTX-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 βCTX-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.” (Lorentzon et al., 2019)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
In a 2018 update, the U.S. Preventive Services Task Force recommended screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older. The Task Force recommended screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in postmenopausal women younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool. The recommendations on osteoporosis screening addressed dual-energy x-ray absorptiometry testing but did not mention bone turnover markers.

Ongoing and Unpublished Clinical Trials
A search of clinicaltrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
On November 25, 2002, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination (NCD) on collagen cross-links. The CMS NCD identified a set of clinical conditions for which collagen cross-links would be considered eligible for coverage. The CMS NCD is limited to urine-based collagen cross-link tests and does not address serum-based collagen cross-link tests.

Medicare Manual: 190.19 - Collagen Crosslinks, Any Method
(Effective 01/01/2003) (Effective/Implementation: Not Applicable); PM AB-02-110
Generally speaking, collagen crosslink testing is useful mostly in “fast losers” of bone. The age when these bone markers can help direct therapy is often pre-Medicare. By the time a fast loser of bone reaches age 65, she will most likely have been stabilized by appropriate therapy or have lost so much bone mass that further testing is useless. Coverage for bone marker assays may be established, however, for younger Medicare beneficiaries and for those men and women who might become fast losers because of some other therapy such as glucocorticoids. Safeguards should be incorporated to prevent excessive use of tests in patients for whom they have no clinical relevance.

Collagen crosslinks testing is used to:
1. Identify individuals with elevated bone resorption, who have osteoporosis in whom response to treatment is being monitored.

2. Predict response (as assessed by bone mass measurements) to FDA approved antiresorptive therapy in postmenopausal women.
3. Assess response to treatment of patients with osteoporosis, Paget's disease or the bone, or risk for osteoporosis where treatment may include FDA approved antiresorptive agents, anti-estrogens or selective estrogens receptor moderators.

Limitations
Because of significant specimen to specimen collagen crosslink physiologic variability (15-20 percent), current recommendations for appropriate utilization include: one or two base-line assays from specified urine collections on separate days; followed by a repeat assay about 3 months after starting anti-resorptive therapy; followed by a repeat assay in 12 months after the 3-month assay; and thereafter not more than annually, unless there is a change in therapy in which circumstance an additional test may be indicated 3 months after the initiation of new therapy.

Some collagen crosslink assays may not be appropriate for use in some disorders, according to FDA labeling restrictions.

In 2001, the *Federal Register* noted that Medicare carriers have discretion to make their own determinations on the medical necessity of serum-based collagen cross-link tests for assessing or monitoring bone loss therapy.[22] The *Federal Register* also noted that the Food and Drug Administration approved the serum-based collagen cross-link tests under 510(k) review, as substantially equivalent to the urine-based collagen cross-link test. It should be noted that the serum-based collagen cross-link tests are more commonly performed than urine collagen cross-link tests.

The Medicare NCD analysis focused on the technical feasibility of collagen cross-links and anticipated outcomes. The discussion above focused on the impact on health outcomes as documented in controlled studies.

Local:
There is no local coverage determination on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 7, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
8/1/14	4/8/14	4/15/14	Policy redone to mirror BCBSA policy, "Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated with High Bone Turnover." Policy title changed from "Serum Osteocalcin" to the above title. Collage crosslinks and serum osteocalcin testing are considered experimental/ investigational. Alkaline phosphatase isoenzyme testing is considered established as this testing may be used for the management of other conditions besides bone loss. Added 84078 to policy.
11/1/15	8/18/15	10/28/15	Routine maintenance. Policy updated to reflect the measurement of CPT codes 82583, 83937 and 84078 as established for the diagnosis of Paget's disease of the bone.
9/1/16	6/21/16	6/21/16	Routine policy maintenance. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine policy maintenance. No change in policy status.
9/1/19	6/18/19		Routine policy maintenance. No change in policy status.
9/1/20	6/16/20		Updated rationale section, references added. No change in policy status.
9/1/21	6/15/21		Routine policy maintenance. No change in policy status.
9/1/22	6/21/22		Routine policy maintenance. No change in policy status.
9/1/23	6/13/23		Routine policy maintenance. Updated the last paragraph under the heading of SUMMARY OF EVIDENCE to reflect/support our stance. Added the following statement: The Endocrine Society guideline recommends the "measurement of serum total alkaline

			phosphatase or, when warranted, a more specific marker of bone formation or bone resorption to assess the response to treatment or evolution of the disease in untreated patients with Paget's disease of the bone." The measurement of serum osteocalcin and collagen crosslinks (serum or urine) bone turnover marker levels has been established. It is a useful diagnostic option for the initial diagnosis and subsequent monitoring of patients with Paget's disease of the bone. The use of serum osteocalcin and collagen crosslinks (serum or urine) bone turnover markers for all other conditions associated with high bone turnover, including but not limited to the monitoring of individuals with primary hyperparathyroidism and renal osteodystrophy, is considered experimental/investigational. Vendor: Avalon In order to align with Avalon, updated MPS, Inclusions/Exclusions, and Rationale section. Updated section summary to reflect EST coverage position of osteoporosis. Added codes 83500 and 83505 as EST. Post JUMP: Updated the first bullet under the MPS to read: The safety and effectiveness of the measurement of alkaline phosphatase isoenzymes have been established. It is a useful option for the diagnosis and monitoring of diseases of the bone, liver and/or endocrine system. Updated the MPS and the below statement under Inclusions to read: Measurement of bone turnover markers** in individuals with Paget's disease of the bone when one of the following is present: (ky)

9/1/24	6/11/24		Routine Maintenance Vendor Managed: Avalon Policy Number: AHS - G2051 – Bone Turnover Markers Testing 6/1/22 (ky)

Next Review Date: 2nd Qtr. 2025

Previous Joint Policy on Serum Osteocalcin
Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/10/02	3/10/02	3/10/02	Joint medical policy established
7/21/05	7/21/05	6/14/05	Scheduled review of policy
1/1/07	11/1/06	9/18/06	Routine maintenance
3/1/08	12/11/07	12/2/07	Routine maintenance
3/1/09	12/9/08	2/2/09	Routine maintenance
11/1/12	8/21/12	8/21/12	Routine maintenance; policy updated to mirror BCBSA policy

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BONE TURNOVER MARKERS FOR DIAGNOSIS AND MANAGEMENT OF OSTEOPOROSIS AND DISEASES ASSOCIATED WITH HIGH BONE TURNOVER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	82523, 83500, 83505, 83937, 84078, and 84080 are covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.