2.04.15 Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated With High Bone Turnover

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Policy Statement

Measurement of bone turnover markers is considered **investigational** to determine fracture risk in patients with osteoporosis or with age-related risk factors for osteoporosis.

Measurement of bone turnover markers is considered **investigational** to determine response to therapy in patients who are being treated for osteoporosis.

Measurement of bone turnover markers is considered **investigational** in the management of patients with conditions associated with high rates of bone turnover, including but not limited to any of the following indications:

I. Paget disease
II. Primary hyperparathyroidism
III. Renal osteodystrophy

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The following CPT codes describe bone turnover marker measurements:

- **82523**: Collagen cross links, any method
- **83937**: Osteocalcin (bone g1a protein)

There is no specific CPT code for bone-specific alkaline phosphatase (B-ALP), but several laboratories' websites identify the following CPT code as being used for the Ostate test:

- **84078:** Phosphatase, alkaline; heat stable (total not included)
- **84080**: Phosphatase, alkaline; isoenzymes

Description

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 or immunoassay. Assessment of bone turnover markers is proposed to supplement bone mineral density 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 bone mineral density can be observed.

Related Policies

- Bone Mineral Density Studies
- Vertebral Fracture Assessment with Densitometry

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the

time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Several tests for bone turnover markers have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k). Examples are listed in Table 1.

Table 1. FDA-Cleared 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

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

Rationale

Background

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. There is interest in the use of bone turnover markers to evaluate age-related osteoporosis, a condition characterized by slow, prolonged bone loss, resulting in an increased risk of fractures at the hip, spine, or wrist. Table 2 summarizes the various bone turnover markers.

Table 2. 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)

Formation Markers	Resorption Markers
	Serum and urinary collagen type I cross-linked C-telopeptide (also referred to as CrossLaps)
	Serum carboxy-terminal telopeptide of type I collagen
	Tartrate-resistant acid phosphatase

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

For bone turnover markers to be considered clinically useful, studies need to demonstrate that tests for these markers are accurate and reliable and that their use can improve health outcomes. For example, to evaluate their utility for diagnosing osteoporosis as an adjunct to bone mineral density (BMD) measurements using dual-energy x-ray absorptiometry, studies would also need to show that bone turnover markers independently predict fracture risk beyond BMD and that the additional information provided by information on bone turnover has the potential to influence treatment decisions and clinical outcomes. Similarly, to be considered useful for monitoring osteoporosis treatment beyond follow-up BMD measurements, bone turnover test results would have to impact the decision to continue or change treatment in a way that improves patient outcomes.

Bone Turnover Markers to Determine Fracture Risk

Clinical Context and Test Purpose

One potential purpose of measuring bone turnover markers in patients who have osteoporosis or who are at risk of agerelated osteoporosis is to inform a decision whether to begin, continue, or discontinue therapy.

The question addressed in this evidence review is: Does the assessment of bone turnover markers improve the net health outcome in individuals with osteoporosis or age-related risk factors for osteoporosis?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with osteoporosis or age-related risk factors for osteoporosis.

Interventions

The test being considered is bone turnover markers as an adjunct to BMD. Variability in the measurement of bone turnover markers is related to a number of factors including sample handling and diurnal variation, postprandial status, menopausal status, exercise, alcohol use, medications, health conditions, and recent fractures.[1,]

Comparators

The following practice is currently being used to make decisions of whether to start, continue, or discontinue therapy: bone density measurements with dual-energy x-ray absorptiometry (DXA).

Fracture risk is primarily based on measurements of bone mineral density (BMD) in conjunction with other genetic and environmental factors, such as a 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. However, it must be emphasized that the presence of bone turnover markers in the serum or urine is not necessarily related to bone loss. For example, even if bone turnover is high, if resorption is balanced with formation, there will be no net bone loss. Bone loss will only occur if resorption exceeds formation. Therefore, bone turnover markers have been primarily studied as an adjunct, not an alternative, to measurements of BMD to estimate fracture risk and document the need for preventive or therapeutic strategies for osteoporosis.

Outcomes

The general outcomes of interest are test validity and morbid events, more specifically, the association between test results and bone health, and the impact of the test results on bone fracture and health.

The beneficial outcome of a true test result is confirming effective treatment. The beneficial outcome of a true-negative test is to modify ineffective treatment.

Harmful outcomes of a false-positive result are not receiving the correct treatment. Harmful outcomes of a false-negative test are receiving unnecessary treatment.

Changes in bone turnover are expected to be observed in 3 months. The impact of changes in treatment on bone strength would be observed in 2 to 5 years.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Systematic reviews have examined the association between bone turnover markers and fracture risk, but have not analyzed the predictive value beyond BMD.[2] For example, a meta-analysis by Johansson et al (2014) focused on procollagen type 1 N-terminal propeptide (PINP) and cross-linked C-telopeptide (CTX) markers and examined their ability to predict future fracture risk. Reviewers included 10 prospective cohort studies in which bone turnover markers were measured at baseline and incident fractures were recorded. Pooled analyses were performed on a subset of these studies. Meta-analysis of 3 studies found a statistically significant association between baseline PINP and subsequent fracture risk (hazard ratio 1.23; 95% confidence interval, 1.09 to 1.39). Similarly, a meta-analysis of 6 studies found an association between CTX and fracture risk (hazard ratio=1.18; 95% 1.09 to 1.29). None of the individual studies adjusted for BMD and, consequently, the pooled analyses do not reflect the ability of bone turnover markers to predict fracture risk beyond BMD.

A systematic review by Biver et al (2012) did not find a statistically significant association between osteocalcin (OC; another bone turnover marker) and fracture risk.[3] When findings from 3 studies were pooled, the mean difference in OC levels in patients with and without vertebral fractures was 1.61 ng/mL (95% confidence interval, -0.59 to 3.81 ng/mL). Both systematic reviews noted a high degree of heterogeneity among the published studies identified.

Prospective and Retrospective Studies

An analysis of the Japanese Population-based Osteoporosis (JPOS) study data by Tamaki et al (2013) included postmenopausal women and adjusted for BMD.[4] The study involved baseline surveys, bone turnover marker assessment and BMD measurements, and 3 follow-ups over 10 years. At baseline, 851 women who participated were ages 50 years or older and eligible for vertebral fracture assessment. Of these, 730 women had BMD measurements taken at the initial examination and at one or more follow-ups. Women with early menopause (i.e., <40 years old),

with a history of illness or medication known to affect bone metabolism, or with incomplete data were excluded. After exclusions, 522 women were evaluated. Over a median follow-up of 10 years, 81 (15.5%) of 522 women were found on imaging to have an incident vertebral fracture. Risk of incident vertebral fractures adjusted for BMD T-scores was significantly associated with several bone turnover markers, specifically alkaline phosphatase (ALP), urinary total deoxypyridinoline, and urinary free deoxypyridinoline. For example, in a multivariate model adjusting for various covariates including femoral neck BMD, the risk of developing a fracture per standard deviation of change in ALP was increased by 33% (relative risk, 1.33; 95% confidence interval, 1.06 to 1.66). Risk of incident vertebral fracture was not significantly associated with other bone turnover markers including OC and CTX. It is not clear how generalizable findings from this study are, given the association between subsequent fracture risk and certain bone turnover markers, and the lack of association between fracture risk and other bone turnover markers. Study analysis also excluded a large number of women due to incomplete data.

Bauer et al (2009) reported on men in a subgroup analysis of prospectively collected data from the Osteoporotic Fractures in Men (MrOS) study also adjusted for BMD.[5] Baseline levels of bone turnover markers were compared in 384 men, ages 65 years or older, who had nonspine fractures over an average follow-up of 5 years, with 885 men without nonspine fracture. A second analysis compared 72 hip fracture cases and 993 controls without hip fracture. After adjusting for age and recruitment site, the association between nonspine fracture and quartile of the bone turnover marker PINP was statistically significant (for each analysis, $p<0.05$ was used). The associations between nonspine fracture and quartiles of the 2 other bone turnover markers, beta C-terminal cross-linked telopeptide of type 1 collagen and tartrate resistant acid phosphatase 5b were not statistically significant. Moreover, in the analysis adjusting only for age and recruitment site, when the highest quartile of bone turnover markers was compared with the lower 3 quartiles, the risk of nonspine and hip fractures was significantly increased for PINP and beta C-terminal cross-linked telopeptide of type 1 collagen, but not tartrate-resistant acid phosphatase 5b. After additional adjustment for baseline BMD, or baseline BMD and other potential confounders, there were no statistically significant relations between any bone turnover marker and fracture risk. The authors concluded that their results did not support the routine use of bone turnover markers to assess fracture risk in older men when measuring hip BMD was an option.

Zhang et al (2019) studied the use of multiple bone turnover markers for diagnosis of osteoporosis in a prospective study of 9053 Chinese post-menopausal women (2464 with osteoporosis and 6589 without osteoporosis).[6] The markers were bone-specific alkaline phosphatase, bone sialoprotein, CTX, osteoprotegerin, OC, and soluble receptor activator of nuclear factor kappa-B ligand. When compared to BMD measured by DXA, no individual marker had sufficient diagnostic accuracy. However, a model using all 6 markers was found to have a sensitivity of 0.99, a specificity of 0.99, and an agreement of 0.978 compared to BMD. Several advantages of using serum BTMs compared to DXA were discussed. The study was funded by the National Natural Science Foundation of China, and there is currently no commercially available panel that includes all 6 markers.

Studies have also reported that bone turnover markers might be used along with other factors to determine who is likely to develop osteoporosis, with the goal of beginning treatment before skeletal deterioration.[7,8] For example, a study by Shieh et al (2019) found that baseline urinary N-telopeptide in combination with age, race/ethnicity, and body mass index was found to predict a significant bone loss in perimenopausal women.[8] No evidence was identified that has evaluated whether earlier treatment reduces fracture risk.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No randomized controlled trials were identified that evaluated the effect of measurement of bone turnover markers on health outcomes.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
To provide clinical utility, bone turnover markers would have to provide information, beyond that offered by BMD measurements, that has an impact on treatment decisions, and/or that leads to improved health outcomes. Bone turnover markers can be measured more frequently than BMD and thus could provide information with clinical utility. For example, biochemical markers of bone turnover might be used to predict the extent of fracture risk reduction when measured 3 to 6 months after starting osteoporosis treatments approved by the U.S. Food and Drug Administration.

Section Summary: Clinical Validity of Bone Turnover Markers and Future Fracture Risk
Few studies have directly addressed whether any bone turnover markers beyond BMD measurements are independent predictors of fracture risk. Some studies have found statistically significant associations between bone turnover markers and fracture risk, but there is insufficient literature on any specific marker. For example, an analysis of MrOS data found a significant association between PINP and risk of nonspine fracture in men, and the JPOS study from Japan found a significant association between ALP, urinary total deoxypyridinoline, and urinary free deoxypyridinoline and risk of incident vertebral fracture in women. Overall, the evidence does not suggest that any bone turnover marker is an independent predictor of fracture risk, beyond BMD.

Bone Turnover Markers to Determine Response to Osteoporosis Treatment
Clinical Context and Test Purpose
Bone turnover markers might provide a more immediate assessment of treatment response and predict a change in BMD in response to treatment. Treatment-related changes in BMD occur very slowly. This fact, coupled with the precision of BMD technologies, has 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 to 6 months of therapy.

The purpose of measuring for bone turnover markers in patients who have suspected osteoporosis is to inform a decision whether to change therapy.

The question addressed in this evidence review is: Does the assessment of bone turnover markers improve the net health outcome in individuals who are being treated for osteoporosis?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are being treated for osteoporosis.

Interventions
The test being considered is bone turnover markers as an indicator of response to therapy. Variability in the measurement of bone turnover markers is related to a number of factors including sample handling and diurnal variation, postprandial status, menopausal status, exercise, alcohol use, medications, health conditions, and recent fractures.[1.]

Comparators
The following practice is currently being used to manage osteoporosis: BMD measurements with DXA.

Outcomes
The general outcomes of interest are test validity and morbid events, more specifically, the association between test results and bone health, and the impact of the test results on bone fracture and health.

The beneficial outcome of a true test result is confirming effective treatment. The beneficial outcome of a true-negative test is to modify ineffective treatment.

Harmful outcomes of a false-positive result are not receiving the correct treatment. Harmful outcomes of a false-negative test are receiving unnecessary treatment.

Changes in bone turnover are expected to be observed in 3 to 6 months. The impact of changes in treatment on bone strength would be observed in 2 to 5 years.

Clinically Valid
Studies have examined the ability of bone turnover markers to evaluate response to osteoporosis treatment.

Randomized Controlled Trials
A subgroup analysis of the randomized Fracture Intervention Trial (FIT, n=6184) by Bauer et al (2006) found that pretreatment levels of the bone turnover marker PINP significantly predicted the anti-fracture efficacy of alendronate.[9.] Over a mean follow-up of 3.2 years, there were 492 nonspine and 294 vertebral fractures. Compared with those in the placebo group, the efficacy of alendronate for reducing nonspine fractures was significantly greater in women who were in the highest tercile of PINP (>56.8 ng/mL) than in those in the lowest tercile (<41.6 ng/mL). Baseline bone turnover rates were not associated with alendronate efficacy in reducing vertebral fractures. The authors indicated that this result needed confirmation in additional studies, and, even if verified, the impact on treatment recommendations was unclear.

Observational Studies
Baxter et al (2013)[10.] reported a retrospective review of 200 patients commencing treatment with bisphosphonates for osteoporosis or osteopenia. Investigators found a statistically significant inverse correlation between change in urine Nterminal telopeptide at 4 months and change in spine BMD at 18 months (r=0.33, p<0.001). There was no significant association between change in urine N-terminal telopeptide and hip BMD.

Section Summary: Clinical Validity of Bone Turnover Markers and Response to Osteoporosis Treatment
The available evidence on the association between any specific bone turnover marker and response to osteoporosis treatment is limited in quantity and quality. While some individual studies have reported positive correlations for markers (e.g., PINP in the FIT trial) a body of evidence in support of any specific marker is lacking. As a result, the evidence does not permit conclusions about whether bone turnover markers are an independent predictor of treatment response.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials RCTs. No RCTs were identified that managed therapy based on results of the test.

Several RCTs have addressed whether measurement of bone turnover markers can improve adherence to oral bisphosphonate treatment. A systematic review by Burch et al (2014) identified 5 RCTs and did not find significant differences in compliance rates between groups that did and did not receive feedback on bone turnover marker test results.[11] Study data were not pooled. Reviewers noted a high baseline compliance rate that limited the studies' ability to detect an impact of feedback. As an example, an industry-sponsored study by Roux et al (2012) from France randomized physicians to manage patients on oral ibandronate given monthly with a collagen cross-links test or usual care.[12] In the collagen cross-links group, bone marker assessment was done at baseline and week 5 for the week 6 visit. A standardized message was delivered to patients regarding a change in CTX since baseline. If the decrease in CTX was more than 30% of the baseline value, patients were told that the treatment effect was optimal. If not, they were told that the treatment effect was suboptimal and given additional advice. Patients told they had a suboptimal response were retested with CTX at week 13 for the week 14 visit. The primary outcome was the proportion of patients who were adherent at 1 year. After 1 year, rates of adherence to ibandronate were 74.8% in the collagen cross-links group and 75.1% in the usual care group; the difference between groups was not statistically significant (p=0.93). There was also no statistically significant difference in the proportion of patients having taken at least 10 of 12 pills (82.4% in the collagen cross-links group vs 80.0% in the usual care group). In this study, monitoring bone markers and providing this information to patients did not improve adherence to oral osteoporosis medication.

Section Summary: Clinical Utility of Bone Turnover Markers in Patients who are Treated for Osteoporosis

There is a limited amount of evidence on the impact of bone turnover markers on the management of osteoporosis. Individual RCTs and a meta-analysis of these RCTs have not found that feedback on bone turnover marker results improves adherence rates. No studies were identified that evaluated whether the use of bone turnover markers leads to management changes that are expected to improve outcomes.

Other Conditions Associated With High Rates of Bone Turnover

Clinical Context and Test Purpose

Bone turnover markers have been evaluated as markers of diseases associated with markedly high levels of bone turnover, such as Paget disease, primary hyperparathyroidism, and renal osteodystrophy. The purpose of measuring bone turnover markers in patients who have conditions associated with high rates of bone turnover is to inform a decision whether to alter management.

The question addressed in this evidence review is: Does the assessment of bone turnover markers improve the net health outcome in individuals who have conditions other than age-related osteoporosis associated with high rates of bone turnover?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who have conditions associated with high rates of bone turnover.

Interventions

The test being considered is bone turnover markers.

Comparators
The following practices are currently being used to manage other conditions associated with high rates of bone turnover: bone density measurements with dual-energy x-ray absorptiometry and bone scintigraphy.

Outcomes
The general outcomes of interest are test validity and morbid events, more specifically, the association between test results and bone health, and the impact of the test results on bone fracture and health. Changes in bone turnover are expected to be observed in 3 months. The impact of changes in treatment on bone strength would be observed within 2 to 5 years.

The beneficial outcome of a true test result is undergoing correct treatment. The beneficial outcome of a true-negative test is to avoid unnecessary or incorrect treatment.

Harmful outcomes of a false-positive result are unnecessary treatment. Harmful outcomes of a false-negative test are not receiving the correct treatment.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

There is little published literature on the use of bone turnover markers in the management of conditions associated with high rates of bone turnover (e.g., primary hyperparathyroidism, Paget disease, renal osteodystrophy), and many available studies were published 10 or more years ago.

Systematic Reviews
A systematic review and meta-analysis by Al Nofal et al (2015) assessed the literature on bone turnover markers in Paget disease.[13] 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, 6 considered both the pre- and posttreatment associations, and 5 included only the posttreatment period. Only one 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, N-terminal telopeptide) and pretreatment disease activity. In a pooled analysis of available data, there was a statistically significant correlation between levels of a bone turnover marker and disease activity after treatment with bisphosphonates (p=0.019). Reviewers did not address the potential impact on the bone turnover measurement on patient management or health outcomes.

Retrospective Studies
A study by Rianon et al (2012) reported on 198 patients with primary hyperparathyroidism who underwent parathyroidectomy.[14] They found a statistically significant association ($p<0.05$) between preoperative serum OC levels and persistent postoperative elevation of parathyroid hormone 6 months after the surgery.

Section Summary: Clinically Valid
There is little published literature on the use of bone turnover markers in the management of conditions associated with high rates of bone turnover (e.g., primary hyperparathyroidism, Paget disease, renal osteodystrophy), and many available studies were published 10 or more years ago. Large prospective trials are needed to establish clinical validity.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive

correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs of bone turnover markers in these conditions have been identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity and evidence that test results would change patient management. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Evidence is insufficient to support that results of bone marker tests would affect patient management, therefore, no inferences can be made about clinical utility.

Section Summary: Clinical Utility
There is a lack of evidence on how the measurement of bone turnover markers can change management or improve health outcomes in patients who have diseases associated with high bone turnover. Although observational studies have demonstrated an association between bone markers and disease activity, the clinical utility of monitoring bone turnover markers for the management of diseases associated with high bone turnover is uncertain.

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 BMD measurements are independent predictors of fracture risk. Studies have suggested that bone turnover marker levels may be independently associated with osteoporosis and fracture risk in some groups, but there is insufficient evidence reporting on an association with any specific marker. Questions remain whether bone turnover markers are sufficiently sensitive to determine reliably individual treatment responses. Overall, the evidence does not suggest that any bone turnover marker is an independent predictor of fracture risk, beyond BMD. The evidence is insufficient 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 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. There is a limited amount of evidence on the impact of bone turnover markers on the management of osteoporosis. Individual RCTs and a meta-analysis of these RCTs have not found that feedback on bone turnover marker improves treatment adherence rates. No studies were identified that evaluated whether the use of bone turnover markers leads to management changes that are expected to improve outcomes. The evidence is insufficient 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. There is a lack of evidence on how the measurement of bone turnover markers can change patient management or improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the remaining sections in Supplemental Information is to provide reference material regarding existing practice guidelines and position statements, U.S. Preventive Services Task Force Recommendations and Medicare National Coverage Decisions and registered, ongoing clinical trials. Inclusion in the Supplemental Information does not imply endorsement and information may not necessarily be used in formulating 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.

The Endocrine Society

In 2019, guidelines from the Endocrine Society recommended 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.[15] 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.

The 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.[16] 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.

National Osteoporosis Foundation

In 2014, the National Osteoporosis Foundation published its guidelines on the prevention and treatment of osteoporosis to prevent fractures.[17] Regarding biochemical markers of bone turnover, the guidelines stated:

"Biochemical markers of bone turnover can

- aid in risk assessment and serve as an additional monitoring tool when treatment is initiated
- be repeated to determine if treatment is producing expected effect."

"Biochemical markers of bone turnover may

- Predict rapidity of bone loss in untreated patients
- 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
- 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
In 2011, a joint statement by the International Society for Clinical Densitometry and the International Osteoporosis Foundation on the Fracture Risk Assessment Model (FRAX) fracture risk prediction algorithms indicated that the "Evidence that bone turnover markers predict fracture risk independent of BMD [bone mineral density] is inconclusive. Therefore, bone turnover markers are not included as risk factors in FRAX."[18]

National Bone Health Alliance
In 2017, recommendations from the National Bone Health Alliance considered N-terminal propeptide of type I procollagen (PINP) and C-terminal telopeptide of type I collagen (CTX-I) as "international reference standards" for bone formation and resorption, respectively.[1] Among the conditions associated with increased bone turnover were primary hyperparathyroidism, vitamin D deficiency, immobility, fracture, and Paget disease; the guidelines also considered diseases associated with low or disassociated bone turnover. The National Bone Health Alliance advised that caregivers control for factors such as food intake, time of sample collection, and handling procedure (i.e., CTX-I assays should be conducted in a fasting state); and that those interpreting the results of bone turnover marker tests be familiar with how uncontrollable factors (i.e., age, comorbidities, medications) may interact with a patient's CTX-I or PINP levels.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force (2018) recommended screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older.[19] 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.

Medicare National Coverage
In November 2002, the Centers for Medicare & Medicaid Services issued a national coverage determination on collagen cross-links.[20] The Centers for Medicare & Medicaid Services identified a set of clinical conditions for which collagen cross-links would be considered eligible for coverage. The decision is limited to urine-based collagen cross-link tests and does not address serum-based collagen cross-link tests.

Previously, the *Federal Register* (2001) noted that Medicare carriers have the discretion to make their own determinations on the medical necessity of serum-based collagen cross-link tests for assessing or monitoring bone loss therapy.[21] The *Federal Register* also noted that the U.S. Food and Drug Administration approved 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.

Note that the Centers for Medicare & Medicaid Services analysis focused on the technical feasibility of collagen crosslinks and anticipated outcomes. The discussion above focused on the impact on health outcomes as documented in controlled studies.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 20210 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	82523	Collagen cross links, any method
	83937	Osteocalcin (bone g1a protein)
	84078	Phosphatase, alkaline; heat stable (total not included)
	84080	Phosphatase, alkaline; isoenzymes
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
12/07/2006	BCBSA Medical Policy adoption
10/01/2010	Policy Revision with title change from Collagen Cross Links as Markers of Bone Turnover
08/23/2013	Title change from Bone Turnover Markers for Osteoporosis with position change. Policy placed on No Further Routin0 e Literature Review and Update status.
01/30/2015	Policy revision without position change

Effective Date	Action
02/01/2017	Policy revision without position change and title change from Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated with High Bone Turnover
02/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
04/01/2020	Annual review. No change to policy statement. Literature review updated.
03/01/2021	Annual review. No change to policy statement. Literature review updated.
03/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated With High Bone Turnover 2.04.15 **Policy Statement:** Measurement of bone turnover markers is considered **investigational** to determine fracture risk in patients with osteoporosis or with age-related risk factors for osteoporosis. Measurement of bone turnover markers is considered **investigational** to determine response to therapy in patients who are being treated for osteoporosis. Measurement of bone turnover markers is considered **investigational** in the management of patients with conditions associated with high rates of bone turnover, including but not limited to any of the following indications: I. Paget disease II. Primary hyperparathyroidism III. Renal osteodystrophy	**Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated With High Bone Turnover 2.04.15** **Policy Statement:** Measurement of bone turnover markers is considered **investigational** to determine fracture risk in patients with osteoporosis or with age-related risk factors for osteoporosis. Measurement of bone turnover markers is considered **investigational** to determine response to therapy in patients who are being treated for osteoporosis. Measurement of bone turnover markers is considered **investigational** in the management of patients with conditions associated with high rates of bone turnover, including but not limited to any of the following indications: I. Paget disease II. Primary hyperparathyroidism III. Renal osteodystrophy