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.

Table 1. Bone Turnover Markers

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

*Current Policy Effective Date: 9/1/22
(See policy history boxes for previous effective dates)
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. 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.

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.

Table 2. Approved Tests for Bone Turnover Markers

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Year</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrilinks®</td>
<td>Metra Biosystems</td>
<td>1995</td>
<td>Collagen type 1 cross-link, pyridinium</td>
</tr>
<tr>
<td>Osteomark®</td>
<td>Ostex International</td>
<td>1996</td>
<td>Cross-linked N-telopeptides of type 1 collagen</td>
</tr>
<tr>
<td>Serum CrossLaps® ELISA</td>
<td>Immunodiagnostic Systems</td>
<td>1999</td>
<td>Hydroxyproline</td>
</tr>
<tr>
<td>Ostase®</td>
<td>Beckman Coulter</td>
<td>2000</td>
<td>Bone-specific alkaline phosphatase</td>
</tr>
<tr>
<td>N-MID Osteocalcin One-Step ELISA</td>
<td>Osteometer Bio Tech</td>
<td>2001</td>
<td>Osteocalcin</td>
</tr>
</tbody>
</table>

ELISA: enzyme-linked immunosorbent assay
Medical Policy Statement

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

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 measurement of serum osteocalcin and collagen crosslinks (serum or urine) bone turnover marker levels is considered experimental/investigational for all other conditions. 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 (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
 Patients with Paget’s disease of the bone for:
 • Initial diagnosis of Paget’s disease
 • Subsequent monitoring and management of patients with Paget’s disease of the bone.

Exclusions:
The use of serum osteocalcin and collagen crosslinks (serum or urine) bone turnover markers for all other conditions, including but not limited to the monitoring of patients with osteoporosis, primary hyperparathyroidism, renal osteodystrophy, or any other conditions.

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  83937  84078  84080

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

Rationale

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 age-related osteoporosis is to inform a decision whether to begin, continue, or discontinue therapy.

The question addressed in this evidence review is: Does 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.

**Comparators**
The following practice is currently being used to manage osteoporosis: bone density measurements with dual-energy x-ray absorptiometry.

**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 undergoing correct treatment. The beneficial outcome of a true-negative test is to avoid an unnecessary or incorrect treatment.
Harmful outcomes of a false-positive result are unnecessary treatment. Harmful outcomes of a false-negative test are not receiving correct 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).

**Bone Turnover Markers and Future Fracture Risk**
Few studies have directly addressed the question whether any bone turnover markers beyond BMD measurements are independent predictors of fracture risk.

**Systematic Reviews**
Systematic reviews have examined the association between bone turnover markers and fracture risk but have not included analyses on the additional predictive value beyond BMD. For example, a 2014 meta-analysis by Johansson et al focused on the markers PINP and CTx 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. A meta-analysis of 3 studies found a statistically significant association between baseline PINP and subsequent fracture risk (hazard ratio [HR], 1.23; 95% CI, 1.09 to 1.39). Similarly, a meta-analysis of 6 studies found an association between CTx and fracture risk (HR=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 2012 systematic review by Biver et al did not find a statistically significant association between OC (another bone turnover marker) and fracture risk. 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% CI, -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**
A 2013 analysis of the Japanese Population-based Osteoporosis (JPOS) study data included postmenopausal women and adjusted for BMD. 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 aged 50 years or older and were eligible for vertebral fracture assessment. Of these, 730 women had BMD measurements taken at the initial examination and at 1 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 and with incomplete data were excluded. After exclusions, 522 women were evaluated. Over a median follow-up period of 10 years, 81 of 522 women (15.5%) were found on imaging to have an incident vertebral fracture. Seventy-eight of the 81 women with radiographically detected vertebral fractures were more than 5 years from menopause at baseline. 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 (tDPD) and urinary free deoxypyridinoline (fDPD). For example, in a
multivariate model adjusting for a variety of covariates including femoral neck BMD, the risk of developing a fracture per SD of change in ALP was increased by 33% (risk ratio, 1.33; 95% CI, 1.06 to 1.66). Risk of incident vertebral fracture was not significantly associated with other bone turnover markers including osteocalcin (OC) and crosslinked C-telopeptide (CTx). It is not clear how generalizable findings from this study are; that is, the association between subsequent fracture risk and certain bone turnover markers, and the lack of association between fracture risk and other bone turnover markers. This study is also limited by the large number of women excluded from analysis 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. Baseline levels of bone turnover markers were compared in 384 men, age 65 years or older, who had non-spine fractures over an average follow-up of 5 years with 885 men without non-spine 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 non-spine fracture and quartile of the bone turnover marker procollagen type 1 N-terminal propeptide (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 (b-CTx) and tartrate-resistant acid phosphatase 5b (TRACP5b) 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 non-spine and hip fractures was significantly increased for PINP and b-CTx but not TRACP5b. After additional adjustment for baseline BMD, or baseline BMD and other potential confounders, there were no statistically significant relationships between any bone turnover marker and fracture risk. The authors concluded that their results do 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). 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. 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. 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 Food and Drug Administration.

**Section Summary: Clinical Validity of Bone Turnover Markers and Future 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 non-spine fracture in men, and the JPOS study from Japan found a significant association between ALP, tDPD, and fDPD and risk of incident vertebral fracture in women. Moreover, there is insufficient evidence that any bone turnover marker is an independent predictor of fracture risk, beyond BMD.

**Bone Turnover Markers and 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.

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 (n=6184) by Bauer et al (2006) found that pretreatment levels of the bone turnover marker PINP significantly predicted the antifracture efficacy of alendronate. Over a mean follow-up of 3.2 years, there were 492 nonspine and 294 vertebral fractures. Compared to 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 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 is not clear.

Observational studies
Baxter et al (2013) 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 N-terminal 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 FIT), 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).

Several randomized controlled trials (RCTs) have addressed the issue of whether measurement of bone turnover markers can improve adherence to oral bisphosphonate treatment. A 2014 systematic review 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. Study data were not pooled. The authors noted a high baseline compliance rate that limited the studies’ ability to detect an impact of feedback. As an example, a 2011 industry-sponsored study by Roux et al from France randomized physicians to manage patients on oral monthly ibandronate with a collagen crosslinks test (CTx) or usual care. In the collagen crosslinks group, bone marker assessment was done at baseline and week 5 for the week 6 visit, a standardized message was delivered to patients regarding change in CTx since baseline. If the decrease in CTx was more than 30% of the baseline value, they were told that the treatment effect was optimal. If not, they were told that the treatment effect was suboptimal, and they were 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 CTx group and 75.1% in the usual care group; the difference between groups was not statistically significant (p=0.93). There was also not a statistically significant difference in the proportion of patients having taken at least 10 of 12 pills; 82.4% in the collagen crosslinks group and 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 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 evaluate whether the use of bone turnover markers lead to management changes that are expected to improve outcomes.
OTHER CONDITIONS ASSOCIATED WITH HIGH RATES OF BONE TURNOVER

Clinical Context and Test Purpose
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 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.

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

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

**Retrospective Studies**
A study by Rianon et al (2012) reported on 198 patients with primary hyperparathyroidism who underwent parathyroidectomy. 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 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 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 are tested with measurement of bone turnover markers, 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 accuracy, test validity, and morbid events. 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 an association with any specific marker. Questions remain about whether bone turnover markers are sufficiently sensitive to reliably determine individual treatment responses. In addition, there is insufficient evidence from controlled studies that bone turnover marker measurement improves adherence to treatment, impacts management decisions, or improves health outcomes (e.g., reducing fracture rates). The evidence is insufficient to determine the effects of the technology on health outcomes. Thus, the use of bone turnover markers for the diagnosis and management of osteoporosis is considered experimental/investigational.

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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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
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.

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. 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 updated their guideline for prevention and treatment of osteoporosis. 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, but studies are underway).

North American Menopause Society
In 2010, the North American Menopause Society issued an updated position statement on management of osteoporosis in postmenopausal women. The statement included the recommendation, “the routine use of biochemical markers of bone turnover in clinical practice is not generally recommended.”

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: “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.”
National Bone Health Alliance
Recommendations from the National Bone Health Alliance (2017) 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. 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
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.21 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.23 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. 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 & Medicaid 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
References


The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2022, the date the research was completed.
<table>
<thead>
<tr>
<th>Policy Effective Date</th>
<th>BCBSM Signature Date</th>
<th>BCN Signature Date</th>
<th>Comments</th>
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<tr>
<td>8/1/14</td>
<td>4/8/14</td>
<td>4/15/14</td>
<td>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.</td>
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<td>11/1/15</td>
<td>8/18/15</td>
<td>10/28/15</td>
<td>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.</td>
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Next Review Date: 2nd Qtr. 2023
## Previous Joint Policy on Serum Osteocalcin
### Medical Policy History

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<td>6/14/05</td>
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<td>8/21/12</td>
<td>8/21/12</td>
<td>Routine maintenance; policy updated to mirror BCBSA policy</td>
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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:

<table>
<thead>
<tr>
<th>Commercial HMO (includes Self-Funded groups unless otherwise specified)</th>
<th>84080 is covered; 82523, 83937 and 84078 are covered for the diagnosis and treatment of Paget's disease of the bone only.</th>
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<tr>
<td>BCNA (Medicare Advantage)</td>
<td>See government section.</td>
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<tr>
<td>BCN65 (Medicare Complementary)</td>
<td>Coinsurance covered if primary Medicare covers the service.</td>
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</table>

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.