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

Policy Number: 2.04.15  Last Review: 5/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Bone Turnover Markers for the Diagnosis and Management of Osteoporosis and Diseases Associated with High Bone Turnover. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
Measurement of bone turnover markers is considered investigational in the diagnosis and management of 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 Paget disease, primary hyperparathyroidism, and renal osteodystrophy.

Description of Procedure or Service

<table>
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<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<td>Individuals:</td>
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<td>With osteoporosis or with risk factors for age-related osteoporosis</td>
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<td>• Measurement of bone turnover markers</td>
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<td>• Morbid events</td>
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Summary
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 (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.

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 whether bone turnover markers are sufficiently sensitive to reliably determine individual treatment responses. In addition, controlled studies do not provide sufficient evidence that bone turnover marker measurement improves adherence to treatment, impacts management decisions, or improves health outcomes (eg, reducing fracture rates). 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 (eg, primary hyperparathyroidism, Paget disease, renal osteodystrophy) who are tested with 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 accuracy, 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 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.

Background
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>
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<tr>
<td>Serum osteocalcin (OC)</td>
<td>Serum and urinary hydroxyproline (Hyp)</td>
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<tr>
<td>Serum total alkaline phosphatase (ALP)</td>
<td>Urinary total pyridinoline (Pyr)</td>
</tr>
<tr>
<td>Serum bone-specific alkaline phosphatase (B-ALP)</td>
<td>Urinary total deoxypyridinoline (d-Pyr)</td>
</tr>
<tr>
<td>Serum procollagen I carboxyterminal propeptide (PICP)</td>
<td>Urinary-free pyridinoline (f-Pyr, also known as Pyrilinks®)</td>
</tr>
<tr>
<td>Serum procollagen type I N-terminal propeptide (PINP)</td>
<td>Urinary-free deoxypyridinoline (f-dPyr, also known as Pyrilinks-D®)</td>
</tr>
<tr>
<td>Bone sialoprotein</td>
<td>Serum and urinary collagen type I cross-linked N-telopeptide (NTx, also referred to as Osteomark®)</td>
</tr>
<tr>
<td></td>
<td>Serum and urinary collagen type I cross-linked C-telopeptide (CTx, also referred to as CrossLaps®)</td>
</tr>
<tr>
<td></td>
<td>Serum carboxyterminal telopeptide of type I collagen (ITCP)</td>
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<tr>
<td></td>
<td>Tartrate-resistant acid phosphatase (TRAP or TRACP)</td>
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</tbody>
</table>

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. 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 also been researched as markers of diseases associated with markedly high levels of bone turnover, such as Paget disease, primary hyperparathyroidism, and renal osteodystrophy.
**Regulatory Status**
Several tests for bone turnover markers have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k). Examples are listed in Table 2.

<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>
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</tbody>
</table>

ELISA: enzyme-linked immunosorbent assay.

**Rationale**
This evidence review was created in July 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 1, 2018.

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.
Diagnosis and Management of Osteoporosis

Clinical Context and Test Purpose
The purpose of measuring for bone turnover markers in patients who have suspected osteoporosis 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 with osteoporosis or age-related risk factors for osteoporosis?

The following PICOTS were used to select literature to inform this review.

Patients
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.

Timing
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.

Setting
The setting is outpatient care by primary care providers.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.
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 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 analyzed the predictive value beyond BMD. 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 [HR], 1.23; 95% confidence interval [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 systematic review by Biver et al (2012) did not find a statistically significant association between osteocalcin (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
An analysis of the Japanese Population-based Osteoporosis (JPOS) study data by Tamaki et al (2013) 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 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 (ie, <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. 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, 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% CI, 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. 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 (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 nonspine 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 relations between any bone turnover marker and fracture risk. 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.

**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 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 and Response to Osteoporosis Treatment**

Studies have examined the ability of bone turnover markers to evaluate response to osteoporosis treatment.
**Systematic Reviews**
A systematic review by Funck-Brentano et al (2011) assessed whether early changes in serum biochemical bone turnover markers predict the efficacy of osteoporosis therapy. Reviewers included 24 studies that presented correlations between bone turnover markers and the outcomes of fracture risk reduction or change in BMD. Five studies (including the Bauer study, previously described) reported on fracture risk, and 20 studies reported on BMD changes. Reviewers discussed study findings qualitatively but did not pool study results. The evidence did not support a correlation between short-term changes in bone turnover markers and fracture risk reduction. In addition, few studies were available on this topic, leading to the conclusion that bone turnover markers “have shown limited value” as a technique to monitor osteoporosis therapy. Subsequently, additional study on this topic was published by Baxter et al (2013). This retrospective review evaluated 200 patients commencing treatment with bisphosphonates for osteoporosis or osteopenia. Investigators found a statistically significant inverse correlation between change in urine NTX 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 NTX and hip BMD.

**Randomized Controlled Trials**
A small randomized trial by Shiraki et al (2009) measured OC levels in response to osteoporosis treatment in 109 postmenopausal women. Authors found that undercarboxylated OC levels in serum were significantly lower at 1 month in the group receiving active treatment for osteoporosis than the control intervention; the implication for fracture prevention was not studied.

Another randomized trial by Abe et al (2008) assessing an osteoporosis treatment (N=43) found that urinary cross-linked N-terminal telopeptides (NTP) provided a more sensitive measure of treatment response than serum levels.

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 antifracture efficacy of alendronate. 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. Authors indicated that this result needed confirmation in additional studies, and, even if verified, the impact on treatment recommendations was unclear.

**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 (eg, PINP in the 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).

**Diagnosis and Management of Osteoporosis**
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, guidelines from the National Osteoporosis Foundation (2014) stated that biochemical markers of bone turnover can 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.\(^\text{10}\).

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.\(^\text{11}\) 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.\(^\text{12}\) 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 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.

**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.

Because the clinical validity of using bone turnover markers to management osteoporosis has not been established, a chain of evidence supporting the clinical utility of these markers cannot be established.

**Section Summary: Clinical Utility of Diagnosis and Management of 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 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**
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 PICOTS were used to select literature to inform this review.

**Patients**
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.

Timing
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.

Setting
The setting is outpatient care by a primary care provider.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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 (eg, 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. 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 (eg, 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 receive 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 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 on an association with any specific marker. Questions remain whether bone turnover markers are sufficiently sensitive to determine reliably individual treatment responses. In addition, controlled studies do not provide sufficient evidence that bone turnover marker measurement improves adherence to treatment, impacts management decisions, or improves health outcomes (eg, reduces fracture rates). 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 (eg, primary hyperparathyroidism, Paget disease, renal osteodystrophy) who receive 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 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

Practice Guidelines and Position Statements

National Osteoporosis Foundation
The National Osteoporosis Foundation updated its guideline on the screening of osteoporosis to prevent fractures. Regarding biochemical markers of bone turnover, the guidelines stated:

“Biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density in untreated patients
- 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.)

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

**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.”

**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 (ie, 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 (ie, 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. 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 (CMS) issued a national coverage determination on collagen cross-links. CMS 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 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 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 CMS 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.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in November 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**REFERENCES**


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**Billing Coding/Physician Documentation Information**

82523  Collagen cross links, any method
83937  Osteocalcin (bone g1a protein)
84080  Phosphatase, alkaline; isoenzymes

**ICD10 Codes**

M81.0-  Osteoporosis without current pathological fracture code range (includes osteoporosis NOS)
M81.8

Z13.820  Encounter for screening for osteoporosis
Z82.62  Family history of osteoporosis

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

5/1/16  New Policy. Considered Investigational.
5/1/17  No policy statement changes.
5/1/18  No policy statement changes.
5/1/19  No policy statement changes.
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