Policy Statement

Measurement of bone turnover markers is considered investigational for any of the following indications:

- Diagnosis and management of osteoporosis
- Management of patients with conditions associated with high rates of bone turnover, including but not limited to:
  - Paget disease
  - Primary hyperparathyroidism
  - Renal osteodystrophy

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:

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

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 (FDA) through the 510(k). 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>ImmunoDiagnostics 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.

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. 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 1 cross-linked N-telopeptide (also referred to as Osteomark)</td>
</tr>
<tr>
<td></td>
<td>Serum and urinary collagen type 1 cross-linked C-telopeptide (also referred to as CrossLaps)</td>
</tr>
<tr>
<td></td>
<td>Serum carboxyterminal telopeptide of type I collagen</td>
</tr>
<tr>
<td></td>
<td>Tartrate-resistant acid phosphatase</td>
</tr>
</tbody>
</table>

Bone Density

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, 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 months of therapy. Bone turnover markers have also been evaluated as markers of diseases associated with markedly high levels of bone turnover, such as Paget disease, primary hyperparathyroidism, and renal osteodystrophy.

**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. The following is a summary of key literature.

**Bone Turnover Markers**

**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.

**Diagnosis and Management of Osteoporosis**

**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. One study conducted in men and another conducted in women are described next.

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 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. 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% confidence interval [CI], 1.06 to 1.66). Risk of incident vertebral fracture was not significantly associated with other bone turnover markers including osteocalcin (OC) and cross-linked C-telopeptide (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.

In men, a 2009 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 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 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.

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 2014 meta-analysis by Johansson et al focused on PINP and 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% 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.
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.

Clinical Validity of Bone Turnover Markers and Response to Osteoporosis Treatment

Studies have examined the ability of bone turnover markers to evaluate response to osteoporosis treatment. For example, 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.

A 2008 randomized trial 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. Another small randomized trial from Japan 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.

A 2011 systematic review by Funck-Brentano et al 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, an 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.

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), 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.
Clinical Utility of 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, the 2014 guidelines from the National Osteoporosis Foundation 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.10

Several randomized controlled trials (RCTs) have addressed 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.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, a 2012 industry-sponsored study by Roux et al 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 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 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.

Management of Other Conditions Associated With High Rates of Bone Turnover

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.

Hyperparathyroidism

One 2012 study by Rianon et al reported on 198 patients with primary hyperparathyroidism who underwent parathyroidectomy.13 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.

Paget Disease

A 2015 systematic review and meta-analysis by Al Nofal et al assessed the literature on bone turnover markers in Paget disease.14 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 post-treatment associations, and five included only the post treatment period. Only 1 study was an RCT; the rest were prospective cohort studies. There was a moderate-to-strong correlation between several bone turnover markers (bone ALP, total ALP, PINP, NTX) and pretreatment disease activity. In a pooled analysis of available data, there was a statistically significant correlation between levels of bone turnover marker and disease activity after treatment with bisphosphonates ($p=0.019$). Reviewers did not address the potential impact on bone turnover measurement on patient management or health outcomes.

Summary of Evidence
For individuals with osteoporosis or risk factors for age-related osteoporosis who receive 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 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 (e.g., 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 (e.g., 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 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.

Supplemental Information
Practice Guidelines and Position Statements

National Osteoporosis Foundation
In 2014, the National Osteoporosis Foundation updated its guideline on the prevention and treatment of osteoporosis. 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 the 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 updated its 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 Osteoporosis Foundation et al**

In 2011, the International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine published a position statement by a joint working group. The group’s aim was to evaluate evidence on using bone turnover markers for fracture risk assessment and monitoring of treatment. The overall conclusion was: “In summary, the available studies relating bone turnover marker changes to fracture risk reduction with osteoporosis treatments are promising. Further studies are needed that take care of sample handling, ensure that bone turnover markers are measured in all available patients, and use the appropriate statistical methods, including an assessment of whether the final bone turnover marker level is a guide to fracture risk.”

**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 (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**

Since November 2016, the U.S. Preventive Services Task Force (USPSTF) recommendations on osteoporosis screening have been in the process of being updated. The 2011 USPSTF recommendations on osteoporosis screening address dual-energy x-ray absorptiometry testing but do not mention bone turnover markers.

**Medicare National Coverage**

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

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 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 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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

References


**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. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**IE**

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>82523</td>
<td>Collagen cross links, any method</td>
</tr>
<tr>
<td></td>
<td>83937</td>
<td>Osteocalcin (bone GlA protein)</td>
</tr>
<tr>
<td></td>
<td>84080</td>
<td>Phosphatase, alkaline; isoenzymes</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Procedure</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
<td></td>
</tr>
</tbody>
</table>
Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/07/2006</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>10/01/2010</td>
<td>Policy Revision with title change from Collagen Cross Links as Markers of Bone Turnover</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/23/2013</td>
<td>Title change from Bone Turnover Markers for Osteoporosis with position change. Policy placed on No Further Routine Literature Review and Update status.</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/30/2015</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2017</td>
<td>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</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**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. Please call (800) 541-6652 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.