Name of Policy:
Bone Turnover Markers for the Diagnosis and Management of Osteoporosis

Policy #:393
Category: Laboratory/Medicine

Latest Review Date: September 2014
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
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 aid in treatment decisions. Bone turnover markers could also potentially be used to evaluate treatment effectiveness before changes in BMD can be observed.

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 osteoblasts and osteoclasts is balanced, but bone loss occurs if the two 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. The table summarizes the various bone-turnover markers.

<table>
<thead>
<tr>
<th>Formation Markers</th>
<th>Resorption Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum osteocalcin (OC)</td>
<td>Serum and urinary hydroxyproline (Hyp)</td>
</tr>
<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 (dPyr)</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 1 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 Cross Laps®)</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 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 two 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.

**Policy:**

**Measurement of bone turnover markers does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** in the diagnosis and management of osteoporosis.

**Measurement of bone turnover markers does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** in the management of patients with conditions associated with high rates of bone turnover, including but not limited to Paget’s disease, primary hyperparathyroidism and renal osteodystrophy.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

In general, to be considered clinically useful, studies need to demonstrate that tests for bone turnover markers are accurate and reliable and that their use can result in improved health outcomes. To evaluate their utility for diagnosing osteoporosis as an adjunct to bone mineral density (BMD) measurements with dual energy x-ray absorptiometry (DEXA), studies would moreover 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 need to impact the decision to continue or change treatment in a way that leads to improved patient outcomes.

An initial literature search was performed in 1999. This policy was updated regularly with a literature review using MEDLINE. Most recently, the literature was searched through July 23, 2014. Following is a summary of key literature on bone turnover markers published to date:

**Diagnosis and Management of Osteoporosis**

**Do bone turnover markers independently predict fracture risk beyond bone mineral density measurements?**

A 2013 analysis of population-based data in Japan included postmenopausal women and adjusted for BMD. The study involved baseline surveys, bone turnover marker assessment and BMD measurements and three 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 one or more follow-ups. Women with early menopause (i.e., younger than 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 included in the analysis.

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 five years from menopause at baseline. Risk of incident vertebral fractures adjusted for BMD T-scores was significantly associated with several bone turnover markers, specifically 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 standard deviation (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 OC and 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.

In men, a sub analysis of prospectively collected data from the Osteoporotic Fractures in Men (MrOS) study also included adjustment of BMD. Baseline levels of bone turnover markers were compared in 384 men, age 65 years or older, who had nonspine fractures over an average follow-up of five 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 two 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 three 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 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 there is the option of measuring hip BMD.

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. The review 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 three 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 six 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 previous systematic review, published in 2012 by Biver et al, did not find a statistically significant association between another bone turnover marker, OC and fracture risk. When findings from three studies were pooled, the mean difference in OC levels in patients with and without vertebral fractures was1.61 ng/mL (95% CI, -0.59 to 3.81). Both systematic reviews noted a high degree of heterogeneity among the published studies identified.

Section Summary
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, 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.

Do bone turnover markers independently predict response to osteoporosis treatment?
Studies have also examined the ability of bone turnover markers to evaluate response to osteoporosis treatment. For example, a subanalysis of the randomized Fracture Intervention Trial (n=6,184) found that pretreatment levels of the bone turnover marker PINP significantly predicted the anti-fracture efficacy of alendronate. Over a mean follow-up of 3.2 years, there were 492 non-spine and 294 vertebral fractures. Compared to those in the placebo group, the efficacy of alendronate for reducing non-spine fractures was significantly greater in women who were in the highest tercile of PINP (>56.8 ng/mL) than those in the lowest tercile (less than
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. A small randomized trial of an osteoporosis treatment (n=43) found that urinary cross-linked N-terminal telopeptides provided a more sensitive measure of treatment response than serum levels. Another small randomized trial from Japan measured levels of osteocalcin in response to osteoporosis treatment in 109 postmenopausal women. The authors found that under-carboxylated osteocalcin (uc-OC) levels in serum was significantly lower at one month in the group receiving active treatment for osteoporosis compared to the control intervention; the implication for fracture prevention was not studied.

A 2011 systematic review by Funck-Brentano and colleagues addressed the issue of whether early changes in serum biochemical bone turnover markers predict the efficacy of osteoporosis therapy. Their review 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, described above) reported on fracture risk and 20 studies reported on BMD changes. The review authors 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. An additional study on this topic was published by Baxter and colleagues in 2013. This was a retrospective review of data on 200 patients commencing treatment with bisphosphonates for osteoporosis or osteopenia requiring treatment. The investigators found statistically significant inverse correlation between change in urine NTx at four months and change in spine BMD at 18 months (Pearson’s correlation [r]: 0.33, p<0.0001). There was not a significant association between change in urine NTx and hip BMD.

Section Summary
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, such as PINP in the Fracture Intervention Trial, a body of evidence in support of any specific marker is lacking. Moreover, a systematic review in 2011 concluded that the evidence does not support an association. As a result, the evidence is insufficient to conclude whether bone turnover markers are an independent predictor of treatment response.

Does information provided by bone turnover markers improve treatment decisions and/or improve health outcomes?
To provide clinical utility, bone turnover markers would need to provide information beyond that offered by BMD measurements that has an impact on treatment decisions and/or leads to improved health outcomes. Bone turnover markers can be measured more frequently than BMD and thus could potentially provide information with clinical utility. For example, the 2013 guideline from the National Osteoporosis Foundation states that biochemical markers of bone turnover can be used to predict the extent of fracture risk reduction when measured three to six months after starting FDA-approved osteoporosis treatments.
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 five 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 CTx group, bone marker assessment was done at baseline and week five for the week six 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 one year. After one 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 CTx 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
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.

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, such as Paget’s disease, primary hyperparathyroidism, and renal osteodystrophy. Moreover, very few studies on this topic have been published since 2000. One recent study, by Rainon and colleagues, reported on 198 patients with primary hyperparathyroidism who underwent parathyroidectomy. The authors found a statistically significant association (p<0.05) between pre-operative serum osteocalcin levels and persistent postoperative elevation of parathyroid hormone six months after the surgery. In addition, several studies were identified that tested bone turnover levels in patients with Paget’s disease before and after treatment with bisphosphonates. For example, Alvarez and colleagues found that the mean values of bone markers decreased significantly after bisphosphonate treatment in 31 of 38 patients who completed a three month course of oral bisphosphonates. Bone markers measured in the Alvarez study included serum total alkaline phosphatase (ALP), serum bone-specific alkaline phosphatase (B-ALP), and PINP and urinary hydroxyproline (Hyp), CTx and NTx. No studies were identified that addressed whether bone turnover markers for
these conditions associated with high bone turnover resulted in improved patient management decisions or health outcomes.

**Summary**
The literature suggests 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 for 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, and/or improves health outcomes such as reducing fracture rates. Thus, the use of bone turnover markers for the diagnosis and management of osteoporosis is considered investigational.

There is insufficient evidence that measurement of bone turnover markers improves patient management or health outcomes in patients with conditions associated with high bone turnover including Paget’s disease, primary hyperparathyroidism, and renal osteodystrophy. Thus, bone turnover marker testing for these other conditions is considered investigational.

**Practice Guidelines and Position Statements**
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 three to six 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).

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.”

In 2011, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) published a position statement by a joint IOF-IFCC Bone Marker Standards Working Group. The aim of the group was to evaluate evidence on using bone turnover markers for fracture risk assessment and monitoring of treatment. The group’s 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”.

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 published the following statement:

“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.”

**U.S. Preventive Services Task Force Recommendations**

The U.S. Preventive Services Task Force 2011 recommendations on osteoporosis screening address DXA testing but do not mention bone turnover markers.

**Key Words:**
Bone Turnover Markers, Collagen Cross links, Osteoporosis

**Approved by Governing Bodies:**
Several tests for bone turnover markers have been cleared by the U.S. Food and Drug Administration (FDA) using the 510(k) process.

Collagen cross-links tests:
- 1995: Pyrilinks test (Metra Biosystems, Santa Clara, CA) measures collagen type 1 cross-link, pyridinium
- 1996: Osteomark test (Ostex International, Seattle, WA) measures cross-linked N-telopeptides of type 1 collagen (NTx)
- 1999: Serum Crosslaps One-step ELISA test measures hydroxyproline

Other bone turnover tests:
- 2000: Ostase® (Beckman Coulter) measures bone-specific alkaline phosphatase (B-ALP)
- 2001: N-MID Osteocalcin One-Step ELISA (Osteometer Bio Tech) measures osteocalcin (OC)

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.
Pre-certification requirements: Not applicable
Current Coding:
CPT Codes:
82523  Collagen cross-links, any method
83937  Osteocalcin (bone g1a protein)
84080  Phosphatase, alkaline, isoenzymes

References:

**Policy History:**
Medical Policy Group, February 2011, (2)
Medical Policy Administration Committee, February 2011
Available for comment February 24 through April 11, 2011
Medical Policy Panel, September 2011
Medical Policy Group, September 2011 (2): Key points, References updated
Medical Policy Panel, October 2012
Medical Policy Group, January 2013 (2): 2012 Update to policy statement – added investigational in the management of patients with conditions associated with high rates of bone turnover, including but not limited to Paget’s disease, primary hyperparathyroidism and renal osteodystrophy; Key Points and References also updated.
Medical Policy Administration Committee, February 2013
Available for comment February 21 through April 7, 2013
Medical Policy Panel, October 2013
Medical Policy Group, October 2013 (1): Update to Key Points and References; no change to policy statement
Medical Policy Panel, September 2014
Medical Policy Group, September 2014 (1): Update to Key Points and References; no change to policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.