

Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Other Conditions



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Medical Policy #: 02.04.13

Original Effective Date: October 2007

Reviewed: February 2022

Revised: February 2021

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DESCRIPTION

Bone turnover markers (BTMs) are biochemical markers of either bone formation or bone resorption (measure collagen breakdown products and other molecules released from osteoclasts and osteoblasts during the process of bone resorption and formation). Commercially available tests assess some of these markers in urine and/or serum by high performance liquid chromatography (HPLC) or immunoassay. The use of bone turnover markers (BTMs) is proposed to supplement bone mineral density (BMD) measurements in the diagnosis and the effects of osteoporosis (bone loss and fracture risk), aid in treatment decisions (response/effectiveness) to osteoporosis treatment, improve compliance with treatment, monitor response to osteoporosis treatment and determine whether or when patients should discontinue treatment or whether or when they should resume treatment. Also, bone turnover makers have been considered in the management

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of conditions associated with high bone turnover including but not limited to Paget’s disease, primary hyperparathyroidism, renal osteodystrophy, diabetes and other endocrine disorders, oncologic indications including the monitoring of metastatic disease, rheumatologic conditions, and vitamin D deficiency.

Background Information on 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. The table below summarizes the various bone turnover markers.

Formation Markers	Resorption Markers
Bone sialoprotein	Serum and urinary collagen type I cross-linked C-telopeptide (CTx, also referred to as Cross Laps®)
Serum bone-specific alkaline phosphatase (B-ALP)	Serum and urinary collagen type I cross-linked N-telopeptide (NTx, also referred to as Osteomark®)
Serum osteocalcin (OC)	Serum and urinary hydroxyproline (Hyp)
Serum total alkaline phosphatase (ALP)	Serum carboxyterminal telopeptide of type I collagen (ITCP)
Serum procollagen I carboxyterminal propeptide (PICP)	Tartrate-resistant acid phosphatase (TRAP or TRACP)
Serum procollagen type 1 N-terminal propeptide (PINP)	Urinary-free deoxypyridinoline (f-dPyr, also known as Pyrilinks-D®)
	Urinary-free pyridinoline (f-Pyr, also known as Pyrilinks®)
	Urinary total deoxypyridinoline (d-Pyr)
	Urinary total pyridinoline (Pyr)

Bone turnover makers (BTMs) have been primarily studied as an adjunct, not an alternative, to measurements of bone mineral density (BMD) to estimate fracture risk and document the need for preventive or therapeutic strategies for osteoporosis. 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. The use of bone turnover markers (BTMs) 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 may predict rate

of bone loss and risk of fracture, however, their role in the care of individual patients is not well established. Biologic and assay variability in BTM values has complicated the use in clinical practice:

- There are many different ways to measure these metabolites of collagen. Assay variability and poor standardization have limited the use of BTMs. Also, because BTM results vary with different laboratories patients need to have all their measurements performed in the same laboratory.
- There are a number of physiologic conditions that increase or decrease bone turnover and therefore, alter BTMs and these factors must be considered when interpreting BTMs which include the following:
 - There is diurnal variation in bone turnover and a strong circadian rhythm to several indices of bone remodeling. The serum concentration or urinary excretion of most markers peak around 6 AM and nadirs around 6 PM. The only marker that is not influenced by diurnal variation is serum BSAP (bone specific alkaline phosphatase).
 - Lower body mass index (BMI) and smoking are associated with high bone turnover and, therefore, higher BTMs.
 - BTMs are increased around the time of ovulation and decreased by use of oral contraceptives.
 - Recent food consumption suppresses BTMs.
 - Exercise and physical activity may be associated with decreased bone turnover (lower BTMs).
 - Bone remodeling is important for fracture healing. BTMs remain elevated for up to four months after fracture.

Also, several criteria must be fulfilled for a particular measurement to have value as a marker of BTMs:

- The substance must change in parallel with changes in bone turnover as measured by histomorphometry and calcium kinetics.
- The serum concentration or urinary excretion of the substance must be high in conditions characterized by high bone turnover, such as hyperparathyroidism, hyperthyroidism, and Paget disease of bone.
- The serum concentration or urinary excretion of the substance must be low in conditions characterized by low bone turnover, as occurs after the administration of antiresorptive drugs.

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 content and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. For bone turnover markers (BTMs) 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 to change treatment in a way that improves patient outcomes.

Diagnosis and Management of Osteoporosis

Clinical Context and Test Purpose

One potential purpose of measuring bone turnover markers (BMTs) in patients who have osteoporosis or who are at risk of age-related osteoporosis is to inform a decision whether to begin, continue or discontinue therapy (duration of therapy).

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 (BTMs) as an adjunct to bone mineral density (BMD).

Variability in the measurement of bone turnover markers (BTMs) is related to a number of factors/conditions including sample handling and diurnal variation, postprandial status, menopausal status, exercise, alcohol use, medications, health conditions and recent fractures.

Outcomes

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

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

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

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

Clinically Valid

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

Systematic Reviews

Systematic reviews have examined the association between bone turnover markers and fracture risk but have not analyzed the predictive value beyond bone mineral density (BMD).

(2014) Johansson et al. completed a meta-analysis focused on the performance characteristics of serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) in fracture risk prediction in untreated individuals in prospective cohort studies. Cross-section studies were excluded. Reviewers included 10 prospective cohort studies. 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 bone mineral density (BMD) and, consequently, the pooled analyses do not reflect the ability of bone turnover markers to predict fracture risk beyond BMD.

(2012) Biver et al. completed a systematic review by evaluated bone turnover markers (BTMs) for osteoporotic status assessment for the positive and etiological diagnosis of osteoporosis at baseline, and their predictive value for past asymptomatic vertebral fractures. Conducted meta-analyses on BTMs levels according to osteoporotic status using random effects models. Moderate and negative correlations were found, mainly in postmenopausal women, between BTMs and BMD, especially with bone alkaline phosphatase (bone ALP), osteocalcin, serum C-terminal and urine N-terminal crosslinking telopeptides of type I collagen (sCTX and uNTX). Bone ALP and sCTX levels are higher in osteoporotic patients compared to controls. High levels of bone ALP in primary hyperparathyroidism and low levels of osteocalcin in endogenous hypercorticism are the most relevant data reported in endocrine diseases associated with osteoporosis. High levels of BTMs, especially osteocalcin, bone ALP or sCTX, may be associated with prevalent vertebral fractures. The authors concluded, the diagnosis value of BTMs at baseline in osteoporosis is very low. The interest of BTMs for the etiological diagnostic of secondary osteoporosis has not been demonstrated. Data are lacking to address the interest of BTMs assessment to screen for vertebral fractures in asymptomatic patients with high risk factors of fractures.

Prospective and Retrospective Studies

(2018) Crandall et al. performed a prospective case-control study that included 800 participants (400 cases with hip fracture and 400 matched controls) to determine the associations of serum C-terminal telopeptide of type one collagen (CTX) and serum procollagen type I aminoterminal propeptide (PINP) with hip fracture risk. This study was nested in the Women's Health Initiative (WHI) Observational Study, which enrolled

participants across 40 US clinical centers. Ages for participants were 50-79 years with an absence of serious medical conditions. Information for the participants with hip fractures was collected by annual self-questionnaires but confirmed by medical record review. Participants in the control case group provided 12 hour fasting morning serum samples for CTX and PINP. The author analysis identified the serum CTX and PINP was not significantly associated with risk of hip fracture. Limitations of the study included the inability to adjust for bone mineral density since this study was part of the larger WHI study and no sample stability data regarding the stored serum samples. However, the study had several strengths including prospective design, long term follow-up, medical record follow for fracture information and fasting serum samples. In summary, the authors concluded the results did not support the utility of serum CTX level or PINP level to predict hip fracture risk in women in this age group.

(2013) An analysis of the Japanese Population-based Osteoporosis (JPOS) study data by Tamaki et. al. included postmenopausal women and adjusted for bone mineral density (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.

(2009) Bauer et al. completed a subgroup analysis of prospectively collected data from the Osteoporotic Fractures in Men (MrOS) study to test the hypothesis that men with higher levels of bone turnover would have accelerated bone loss and elevated risk of fracture. Baseline levels of bone turnover markers were compared in 384 men, ages 65 years or older, who had non-spine fractures over an average follow-up of 5 years, with 885 men without non-spine fracture. A second analysis compared 72 hip fracture cases

and 993 controls without hip fracture. After adjusting for age and recruitment site, the association between non-spine fracture and quartile of the bone turnover marker procollagen type 1 N-terminal propeptide (PINP) was statistically significant (for each analysis, $p < 0.05$ was used). The associations between non-spine fracture and quartiles of the 2 other bone turnover markers, beta C-terminal cross-linked telopeptide of type 1 collagen (b-CTX) and tartrate-resistant acid phosphatase 5b (TRACP5b) were not statistically significant. Moreover, in the analysis adjusting only for age and recruitment site, when the highest quartile of bone turnover markers was compared with the lower 3 quartiles, the risk of non-spine and hip fractures was significantly increased for PINP and b-CTX, but not TRACP5b. After additional adjustment for baseline bone mineral density (BMD), or baseline BMD and other potential confounders, there were no statistically significant relations between any bone turnover marker and fracture risk. The authors concluded in this large prospective study of contemporary bone turnover markers (BTM), bone loss, and fracture in older men, it found that elevated serum levels of PINP, BCTX, and TRACP5b are associated with higher rates of hip bone loss, but the associations were insufficient strength to accurately predict bone loss in any individual subject. Although the data suggested that higher serum of PINP and BCTX at baseline are associated with an increased risk of subsequent hip and non-spine fracture in older men, none of the relationships between BTMs and fracture risk were statistically significant after accounting for baseline BMD. Additional prospective studies are warranted, particularly with novel biomarkers, but these results suggest that a single serum measurement of PINP, BCTX or TRACP5b does not strongly predict future fracture risk in men and should not be incorporated into evolving risk stratification methods.

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 outcomes can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

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

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

To provide clinical utility, bone turnover markers would have to provide information, beyond that offered by BMD measurements, that has an impact on treatment decisions, and/or that leads to improved health outcomes. Bone turnover markers can be measured more frequently than BMD and thus could provide information with clinical utility. For example, biochemical markers of bone turnover might be used to predict the extent of

fracture risk reduction when measured 3 to 6 months after starting osteoporosis treatments approved by the Food and Drug Administration.

(2017) Greenbelt et al. in a systematic review summarized the utility of bone turnover markers (BTMs) in the clinical management of osteoporosis, focusing primarily on postmenopausal osteoporosis. Testing using BTMs has to take into account the large number of preanalytic factors and comorbid clinical conditions influencing BTM levels. BTMs respond rapidly to changes in bone physiology, therefore, they have utility in determining patient response to and compliance with therapies for osteoporosis. However, they concluded that although BTMs are a useful adjunct for the diagnosis and therapeutic monitoring of bone metabolic disorders, their use has to be tempered by the known limitations in their clinical utility and preanalytic variables complicating interpretation. Glendenning et al. (2018) drew similar conclusions regarding the clinical usage of BTMs, noting that data is inconsistent.

Section Summary

Bone turnover markers (BTMs) are predictive of the rate of bone loss and in some studies risk of fracture, however, individual rates of bone loss and fracture are variable, limiting the usefulness of BTMs in predicting an individual's fracture risk. Based on limited evidence in the literature there currently is no clinical utility for use BTMs in selecting candidates for bone density testing or for osteoporosis therapy. The decision to measure bone density should be based upon age and the presence of clinical risk factors for fracture. Similarly, the decision to treat patients should be based upon fracture risk assessment using bone mineral density (BMD) and clinical risk factors. Also, biologic and assay variability in BTM values has complicated their use in clinical practice.

Bone Turnover Markers and Monitoring Response to Osteoporosis Treatment

Clinical Context and Test Purpose

Bone turnover makers might provide a more immediate assessment of treatment response and predict a change in bone mineral density (BMD) in response to treatment. Treatment-related changes in BMD occur very slowly. This fact, coupled with the precision of BMD technologies, has suggested that clinically significant changes in BMD could not be reliably detected until at least 2 years. In contrast, changes in bone turnover markers could be anticipated after 3 to 6 months of therapy.

The purpose of measuring for bone turnover markers (BTMs) in patients who have osteoporosis is to inform a decision on the effectiveness/response of the osteoporosis therapy, compliance of therapy, and duration of therapy (whether or when therapy should be discontinued and whether or when therapy should be resumed).

Patients

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

Interventions

The test being considered is bone turnover markers (BTMs) as an indicator of effectiveness/response to therapy, compliance of therapy, and duration of therapy (whether or when therapy should be discontinued and whether or when therapy should be resumed). The variability in the measurement of bone turnover markers is related to a number of factors including sample handling and diurnal variation, postprandial status, menopausal status, exercise, alcohol use, medications, health conditions, and recent fractures.

Comparators

The following practice is currently being used to manage osteoporosis: BMD (bone mineral density) and DXA.

Outcomes

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

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

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

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

Clinically Valid

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

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 of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

To provide clinical utility, bone turnover markers would have to provide information beyond that offered by bone mineral density (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.

Several randomized controlled trials (RCTs) have addressed whether measurement of bone turnover markers can improve adherence to oral bisphosphonate treatment. A 2014 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. 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. 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 versus 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

While bone turnover markers (BTMs) may show a response to osteoporosis treatments, the optimal threshold for each marker is not well established or standardized. Their role in monitoring osteoporosis therapy relies upon defining the threshold reduction in BTM to attain optimal effects (i.e. fracture reduction), such thresholds are not universally accepted. While there are a number of approaches for monitoring response to antiresorptive therapy, there is no consensus on the optimal approach, and there are no prospective trials to define how to best incorporate markers into monitoring strategies. Also, biologic and assay variability in BTM values has complicated their use in clinical practice. There is also an interest in using BTMs to determine whether or when patients should discontinue bisphosphonates and whether or when they should resume therapy, however, there is currently no data to support this approach.

Other Conditions Associated with High Rates of Bone Turnover

Clinical Context and Test Purpose

Bone turnover markers (BTMs) have been evaluated as markers of diseases associated with markedly high levels of bone turnover, such as Paget disease, primary hyperparathyroidism, and renal osteodystrophy, diabetes and other endocrine disorders,

oncologic indications including the monitoring of metastatic disease, rheumatologic conditions and vitamin D deficiency. 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.

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 (BTMs).

Comparators

The following practices are currently being used to manage other conditions associated with high rates of bone turnover: bone density measurements (BMD) 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 test results on bone fracture and health.

The beneficial outcome of a true test 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 are not receiving correct treatment.

Timing

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

Clinically Valid

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

There is little published literature on use of bone turnover markers (BTMs) in the management of conditions associated with high rates of bone turnover such as primary hyperparathyroidism, Paget disease, renal osteodystrophy, diabetes and other endocrine disorders, oncologic indications including the monitoring of metastatic disease, rheumatologic conditions and vitamin D deficiency and many available studies were published 10 or more years ago.

Retrospective Studies

(2012) One study by Rianon et al. 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. Authors concluded that research with longer follow-up in patients with no known baseline chronic kidney disease stratified by high versus normal preoperative serum creatinine is recommended.

Systematic Review

(2015) Al Nofal et al. completed a systematic review and meta-analysis which 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.

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 of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because there are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

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

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.

(2017) Greenblatt et al. completed a systematic review regarding bone turnover markers (BTMs) in the diagnosis and monitoring of metabolic bone disease to include the following conditions associated with high rates of bone turnover: renal disease (renal osteodystrophy and chronic kidney disease); oncologic indications including the

monitoring of metastatic disease; rheumatologic conditions (rheumatoid arthritis); Paget's disease; and secondary bone loss caused by diabetes, hyperparathyroidism and vitamin D deficiency that can predispose an individual to risk of fractures. Currently the literature is limited in the use of BTMs for identifying patients at risk of rapid bone loss. Comorbid clinical conditions can alter the relationship between BTMs to predict fracture risk, one of the best studied examples, BMD measurements underestimate fracture risk in individuals with diabetes and how to best apply BTMs to estimate fracture risk in diabetic patients represents an area of active investigation. Despite findings linking increased concentrations of resorptive BTMs and fracture risk for conditions associated with high rates of bone turnover, few data exist regarding the utility of such measurement in routine clinical practice. The author concluded while BTMs may be a useful adjunct to diagnosis and therapeutic monitoring of bone metabolic disorders, their use has to be tempered by the known limitations in their clinical utility and preanalytic variables complicating interpretation.

Section Summary

There is lack of evidence on how measurement of bone turnover markers can change management or improve health outcomes in patients who have disease/conditions associated with high bone turnover. Despite findings linking increased concentrations of resorptive BTMs and fracture risk for conditions associated with high rates of bone turnover, few data exist regarding the utility of such measurement in routine clinical practice. Biologic and assay variability in BTM values has also complicated their use in clinical practice.

Summary of Evidence

Bone turnover markers (BTMs) in the serum or urine are sometimes used to assess risk of fracture, predict bone loss or assess response to antiresorptive therapy. BTMs such as pyridinoline, telopeptides and urinary cross-linked N-telopeptide of type I collagen (NTx) (which measure bone resorption) and osteocalcin and bone alkaline phosphatase (which measure bone formation) are obtained through minimally invasive tests involving serum and urine, making BTMs an attractive method for determining risk of fracture especially for osteoporosis management. Specifically, the information obtained could potentially be used to measure the rate of bone loss, assist in determining osteoporosis management, monitor changes in bone metabolism and density resulting from therapy, and manage osteoporosis therapy as needed for the individual patient. However, BTMs are controversial because of the complexity of interpreting the values for individual patients related to the intricacies inherent in bone metabolism, and the lack of standardization, which has led to unacceptable levels of variation between processing laboratories.

While bone turnover markers (BTMs) may show a response to osteoporosis treatments, the optimal threshold for each marker is not well established or standardized. Their role in monitoring osteoporosis therapy relies upon defining the threshold reduction in BTM to attain optimal effects (i.e., fracture reduction), such thresholds are not universally accepted. While there are a number of approaches for monitoring response to

antiresorptive therapy, there is no consensus on the optimal approach, and there are no prospective trials to define how to best incorporate markers into monitoring strategies. Also, biologic and assay variability in BTM values has complicated their use in clinical practice. There is also an interest in using BTMs to determine whether or when patients should discontinue bisphosphonates and whether or when they should resume therapy, however, there is currently no data to support this approach. 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, diabetes and other endocrine disorders, oncologic indications including the monitoring of metastatic disease, rheumatologic conditions and vitamin D deficiency) who receive measurement of bone turnover markers (BTMs), despite findings linking increased concentrations of resorptive BTMs and fracture risk for conditions associated with high rates of bone turnover, few data exist regarding the utility of such measurement in routine clinical practice. Biologic and assay variability in BTM values has also complicated their use in clinical practice. There is a lack of evidence on how the measurement of bone turnover markers (BTMs) can change patient management or improve net health outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)

(2020) The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) has a clinical practice guideline for the diagnosis and treatment of postmenopausal osteoporosis, the AACE and ACE remark that Bone turnover markers (BTMs) provide a dynamic assessment of skeletal activity and are useful modalities for skeletal assessment. Although they cannot be used to diagnose osteoporosis, elevated levels can predict more rapid rates of bone loss and are associated with increased fracture risk independent of BMD in some studies. Problems with the use of BTMs include their high cost (and variable insurance coverage), lack of appropriate reference ranges reported by commercial labs, and the influence of renal insufficiency on all markers except bone-specific alkaline phosphatase. Some experts routinely utilize BTMs in clinical practice, while others do not.

Recommendations include the following:

- Consider using bone turnover markers in the initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk (Grade A; BEL 1).
- Consider using bone turnover markers (BTMs) for assessment of patient compliance and efficacy of therapy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction, and

- significant increases indicate good response to anabolic therapy (Grade B; BEL 1, adjusted down due to limited evidence).
- Consider bone turnover markers at or below the median value for premenopausal women as a target for response to therapy for patients taking antiresorptive agents. Consider significant increases in bone formation markers as a pharmacologic response to anabolic therapy (Grade B; BEL 1, adjusted down due to limited evidence).
 - Because of the high prevalence of causes of secondary osteoporosis even in apparently healthy, postmenopausal women, laboratory testing should be considered for all women with osteoporosis. This is reasonable, as a few simple laboratory tests provided useful information in 40 to 85% of women who did not have clinical evidence of secondary osteoporosis in several studies. If medical history, physical findings, or laboratory test results suggest causes of secondary osteoporosis, additional laboratory evaluation is warranted and may include, but is not limited to a complete blood count, comprehensive metabolic panel, 25-hydroxyvitamin D (25[OH]D), intact parathyroid hormone (PTH), phosphate, and a 24-hour urine collection for calcium, sodium, and creatinine. The 24-hour urine calcium collection must occur after the patient is replete of vitamin D and has been on a reasonable calcium intake (1,000 to 1,200 mg/d) for at least 2 weeks. If the patient is receiving thyroid hormone or there is a suspicion for hyperthyroidism, thyroid-stimulating hormone should also be obtained. Celiac antibodies or serum/urine protein electrophoresis could also be obtained.

(Accessed February 2022)

American College of Obstetrician and Gynecologists (ACOG)

(2021) The American College of Obstetrician and Gynecologists (ACOG) Clinical Practice Guideline for Osteoporosis Prevention, Screening and Diagnosis does not have a recommendation for the use of biochemical markers (bone turnover markers) to predict or treat bone turnover in osteoporosis. *(Accessed February 2022)*

The Endocrine Society

(2020) The Endocrine Society has a Pharmacological Management of Osteoporosis in Postmenopausal Women Guideline which states the following:

- In postmenopausal women with osteoporosis who are at high risk for osteoporotic fractures, we recommend using denosumab as an alternative initial treatment.
 - Technical remark: The recommended dosage is 60 mg subcutaneously every 6 months. The effects of denosumab on bone remodeling, reflected in bone turnover markers, reverse after 6 months if the drug is not taken on schedule. Thus, a drug holiday or treatment interruption is not recommended with this agent.
- In postmenopausal women with a low bone mineral density and at high risk of fractures who are being treated for osteoporosis, we suggest monitoring the bone mineral density by dual energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment.

- Technical remark: Monitoring bone turnover markers (serum C-terminal crosslinking telopeptide for antiresorptive therapy or procollagen type 1 N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy.
- In postmenopausal women with a low bone mineral density and at high risk of fractures who are being treated for osteoporosis, we suggest monitoring the bone mineral density by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment.
 - Technical remark: Monitoring bone turnover markers (serum C-terminal crosslinking telopeptide for antiresorptive therapy or procollagen type N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy.

(Accessed February 2022)

International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

(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 to 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." *(Accessed February 2022)*

International Society for Clinical Densitometry and the International Osteoporosis Foundation (IOF)

(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." *(Accessed February 2022)*

National Osteoporosis Foundation (NOF)

(2014) The National Osteoporosis Foundation has a guideline for prevention and treatment of osteoporosis regarding biochemical markers of bone turnover, the guideline states:

Biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density.
- Predict extent of fracture risk reduction when repeated after 3-6 months of treatment with FDA-approved therapies.
- Predict magnitude of BMD increases with FDA-approved therapies.
- Predict rapidity of bone loss.

- Help determine adequacy of patient compliance and persistence with osteoporosis therapy. Help determine duration of “drug holiday” and when and if medication should be restarted (Data are quite limited to support this use, but studies are underway).

(Accessed February 2022)

National Institute for Health Care Excellence (NICE)

Nice provided two different individual research recommendations for bone turnover markers:

- (2019) What is the clinical utility of bone turnover markers in the diagnosis and management of primary hyperparathyroidism?
 - The committee acknowledged the potential of bone turnover markers to enable earlier and more accurate diagnosis of primary hyperparathyroidism but were unable to make a recommendation because of a lack of evidence. They therefore made a research recommendation on bone turnover markers. *(Accessed February 2022)*
- (2019) Follow-up after surgery
 - The committee acknowledged the potential of bone turnover markers to check bone health after surgery for primary hyperparathyroidism but were unable to make a recommendation because of a lack of evidence. They therefore made a research recommendation on bone turnover markers. *(Accessed February 2022)*

North American Menopause Society (NAMS)

(2021) The North American Menopause Society issued a position statement on the management of osteoporosis in postmenopausal women. The statement included the following recommendation,

- “Bone turnover markers are serum tests that reflect either bone resorption by osteoclasts (fasting serum C-telopeptide of type I collagen) or bone formation by osteoblasts (bone specific alkaline phosphatase or serum procollagen type I N-terminal propeptide) Bone turnover markers cannot diagnose osteoporosis and have varying ability to predict fracture risk in clinical trials. Bone turnover markers have been used primarily in clinical trials to demonstrate group responses to treatment. Although used by some osteoporosis specialists, the routine use of bone turnover markers in the evaluation of patients with osteoporosis is not recommended. *(Accessed February 2022)*

U.S. Preventative Services Task Force

(2011, Updated 2018) The U.S. Preventative Services Task Force (USPSTF) recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older and in postmenopausal women younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool.

Clinical considerations of the recommendation states, the most commonly used bone measurement test used to screen for osteoporosis is central DXA. The screening testing information does not mention the use of bone turnover markers. (*Accessed February 2022*)

Regulatory Status

Several tests for bone turnover markers have been cleared by the U.S. Food and Drug Administration (FDA) using the 510(k) process, examples include but are not limited to are listed below:

Test	Manufacturer	Description
N-MID Osteocalcin One-step ELISA	Osteometer Bio Tech	Measures osteocalcin (OC)
Ostase®	Beckman Coulter	Measures bone-specific alkaline phosphatase (B-ALP).
Osteomark®	Ostex International, Seattle, WA	Measures cross-linked N-telopeptides of type 1 collagen (NTx)
Pyrilinks®	Metra Biosystems, Santa Clara, CA	Measures collagen type 1 cross-link, pyridium
Serum Crosslaps® One-step ELISA	Immunodiagnostic Systems	Test measures hydroxyproline

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

PRIOR APPROVAL

Not applicable.

POLICY

Osteoporosis Fracture Risk

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

While bone turnover markers (BTMs) may show a response to osteoporosis treatments, the optimal threshold for each marker is not well established or standardized. Their role in monitoring osteoporosis therapy relies upon defining the threshold reduction in bone turnover markers (BTM) to attain optimal effects (i.e., fracture reduction), such thresholds are not universally accepted. While there are a number of approaches for monitoring response to antiresorptive therapy, there is no consensus on the optimal approach, and there are no prospective trials to define how to best incorporate markers

into monitoring strategies. Also, biologic and assay variability in bone turnover markers (BTM) values has complicated their use in clinical practice. There is also an interest in using bone turnover markers (BTMs) to determine whether or when patients should discontinue bisphosphonates and whether or when they should resume therapy, however, there is currently no data to support this approach. The evidence is insufficient to determine the effects of the technology on health outcomes.

Osteoporosis Therapy

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

While bone turnover markers (BTMs) may show a response to osteoporosis treatments, the optimal threshold for each marker is not well established or standardized. Their role in monitoring osteoporosis therapy relies upon defining the threshold reduction in bone turnover markers (BTM) to attain optimal effects (i.e., fracture reduction), such thresholds are not universally accepted. While there are a number of approaches for monitoring response to antiresorptive therapy, there is no consensus on the optimal approach, and there are no prospective trials to define how to best incorporate markers into monitoring strategies. Also, biologic and assay variability in bone turnover markers (BTM) values has complicated their use in clinical practice. There is also an interest in using bone turnover markers (BTMs) to determine whether or when patients should discontinue bisphosphonates and whether or when they should resume therapy, however, there is currently no data to support this approach. The evidence is insufficient to determine the effects of the technology on health outcomes.

Conditions Associated with High Rates of Bone Turnover

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 the following:

- Diabetes
- Oncologic indications including the monitoring of metastatic disease
- Paget disease
- Primary hyperparathyroidism
- Renal osteodystrophy
- Rheumatologic conditions
- Vitamin D deficiency

For individuals with conditions associated with high rates of bone turnover other than age related osteoporosis who receive measurement of bone turnover markers (BTMs), despite findings linking increased concentrations of resorptive bone turnover markers (BTMs) and fracture risk for these conditions, few data exist regarding the clinical utility of such measurement in routine clinical practice. Biologic and assay variability in bone turnover maker (BTM) values has also complicated their use in clinical practice. There is a lack of evidence on how the measurement of bone turnover markers (BTMs) can change patient

management or improve net health outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 82523 collagen cross links, any method
- 83937 osteocalcin (bone gla protein)

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POLICY HISTORY

Date	Reason	Action
February 2022	Annual Review	Policy Renewed
February 2021	Annual Review	Policy Revised
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Renewed
February 2018	Annual Review	Policy Renewed
February 2017	Annual Review	Policy Renewed
February 2016	Annual Review	Policy Revised
March 2015	Annual Review	Policy Revised
April 2014	Annual Review	Policy Revised
May 2013	Annual Review	Policy Revised
May 2012	Annual Review	Policy Renewed
August 2011	Annual Review	Policy Revised

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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Medical Policy Analyst
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