Corporate Medical Policy

Bone Turnover Markers Testing AHS – G2051

File Name: bone_turnover_markers_testing
Origination: 01/01/2019
Last CAP Review: n/a
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Last Review: 12/2019

Description of Procedure or Service

Definition
Bone metabolism involves a continual, dynamic equilibrium between bone growth and resorption. Bone turnover markers are biochemical markers for assessment of bone formation or bone resorption. These markers may be useful in determining risk of fracture (Rosen, 2018; Talwar, 2017).

Bone formation markers:
• Serum bone-specific alkaline phosphatase
• Serum osteocalcin
• Serum type 1 procollagen (C-terminal/N-terminal): C1NP or P1NP

Bone resorption markers:
• Urinary hydroxyproline
• Urinary total pyridinoline (PYD)
• Urinary free deoxypyridinoline (DPD)
• Urinary collagen type 1 cross-linked N-telopeptide (NTX)
• Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)
• Bone sialoprotein (BSP)
• Tartrate-resistant acid phosphatase 5b (TRACP5b)
• Cathepsin K

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

The measurement of bone turnover markers for the diagnosis and management of osteoporosis and in the management of patients with conditions associated with high rates of bone turnover is not covered

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When measurement of bone turnover markers is covered
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Not applicable.

**When measurement of bone turnover markers is not covered**

The measurement of bone turnover markers in the diagnosis and management of osteoporosis is not covered.

The measurement of bone turnover markers 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 is not covered.

Note 1: Bone turnover markers include (Rosen, 2018; Talwar, 2017):

1. Bone formation markers:
   a. Serum bone–specific alkaline phosphatase
   b. Serum osteocalcin
   c. Serum type 1 procollagen (C-terminal/N-terminal): C1NP or P1NP

2. Bone resorption markers:
   a. Urinary hydroxyproline
   b. Urinary total pyridinoline (PYD)
   c. Urinary free deoxypyridinoline (DPD)
   d. Urinary collagen type 1 cross-linked N-telopeptide (NTX)
   e. Urinary or serum collagen type 1 cross-linked C-telopeptide (CTX)
   f. Bone sialoprotein (BSP)
   g. Tartrate-resistant acid phosphatase 5b (TRACP5b)
   h. Cathepsin K

**Policy Guidelines**

**Background**

Osteoporosis is a thinning of bone, with a reduction in mass, due to calcium depletion and loss of bone protein. The International Osteoporosis Foundation (2015) provides the following statistics regarding osteoporosis:

- Osteoporosis and low bone mass are currently estimated to be a major public health threat for almost 44 million U.S. women and men aged 50 and older in the United States
- The 44 million people with either osteoporosis or low bone mass represent 55 percent of the people aged 50 and older in the United States
- By the year 2010, it is estimated that more than 52 million women and men in this same age category will be affected and, if current trends continue, the figure will climb to more than 61 million by 2020
- In 2002, it is estimated that more than 10 million people already have osteoporosis. Approximately eighty percent of these people are women. This figure will rise to almost 12 million individuals by 2010 and to approximately 14 million by 2020 if additional efforts are not made to stem this disease, which may be largely prevented with lifestyle considerations and treatment when appropriate

The resorption and reformation of bone “is important for repair of microfractures and to allow modification of structure in response to stress and other biomechanical forces. Bone formation is normally tightly coupled to bone resorption, so that bone mass does not change. Bone diseases occur when formation and resorption are uncoupled” (Rosen, 2018). The exact role of biochemical markers of bone turnover in the management of metabolic bone diseases remains a topic of controversy (Cavalier et al., 2016).
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Several studies show that bone turnover markers show promise in predicting bone loss rate. BTMs can also contribute to a better appraisal of the underlying pathophysiological process, the dynamics of bone remodeling and, in some cases, to monitor the activity of medicines that interfere either with bone formation or bone resorption (Kling, Clarke, & Sandhu, 2014).

Analytical Validity
Seibel et al (2001) described the results of an international proficiency testing program for biochemical bone markers among clinical laboratories finding that “analytical results showed both systematic and nonsystematic deviations. In identical samples, results obtained for the same marker by the same method differed up to 7.3-fold. In urine-based assays, correction for urinary creatinine slightly increased CVs.”

Although automated platforms have substantially improved the analytical variability of bone turnover markers, reproducibility still varies substantially (Hlaing & Compston, 2014).

Schafer et al (2010) assessed the laboratory reproducibility of urine N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP), and found that “Longitudinal coefficients of variation (CVs) ranged from 5.4% to 37.6% for NTX and from 3.1% to 23.6% for BAP. Within-run CVs ranged from 1.5% to 17.2% for NTX.”

The National Bone Health Alliance executed a project to standardize bone turnover marker collection procedures and reduce pre-analytical variability (Bauer et al., 2012). The results of that project and the IOF and IFCC Bone Marker Standards Working Group identification of PINP and CTX-I in blood to be the reference markers of bone turnover for the fracture risk prediction and monitoring of osteoporosis treatment (Vasikaran, Eastell, et al., 2011) have resulted in recommendations for standard sample handling and patient preparation (Szulc, Naylor, Hoyle, Eastell, & Leary, 2017).

Standardization and harmonization of clinical assays for bone turnover markers; serum assay for CTx and P1NP are ongoing (IFCC, 2018).

Clinical Validity and Utility
Johansson et al (2014) “used an updated systematic review to examine 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. We excluded cross-sectional studies. Ten potentially eligible publications were identified and six included in the meta-analysis. There was a significant association between s-PINP and the risk of fracture. The hazard ratio per SD increase in s-PINP (gradient of risk [GR]) was 1.23 (95% CI 1.09-1.39) for men and women combined unadjusted for bone mineral density. There was also a significant association between s-CTX and risk of fracture, GR = 1.18 (95% CI 1.05-1.34) unadjusted for bone mineral density. For the outcome of hip fracture, the association between s-CTX and risk of fracture was slightly higher, 1.23 (95% CI 1.04-1.47). Thus, there is a modest but significant association between BTMs and risk of future fractures.”

In 2017 Morris et al found that: “Current evidence continues to support the potential for bone turnover markers (BTM) to provide clinically useful information particularly for monitoring the efficacy of osteoporosis treatment. Many of the limitations identified earlier remain, principally in regard to the relationship between BTM and incident fractures. Important data are now available on reference interval values for CTX and PINP across a range of geographic regions and for individual clinical assays” (Morris et al., 2017).

The most recent review of bone turnover markers for the journal of the International Federation of Clinical Chemistry and Laboratory Medicine (Bhattoo, 2018) found that “Although quite sensitive to a multitude of exogenous and endogenous pre-analytical factors, bone markers are best used in monitoring anti-osteoporosis therapy efficacy and compliance. Combination of BMD measurement by DEXA with biochemical markers of bone turnover levels, at least one bone
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resorption and one bone formation marker, may potentially improve early detection of individuals at increased risk for bone loss and eventually non-traumatic bone fracture. Furthermore, they have widespread clinical utility in osteoporosis, renal osteodystrophy, certain oncological conditions and rheumatic diseases.”

State and Federal Regulations, as applicable
Several tests for bone turnover markers have been cleared by the U.S. Food and Drug Administration (FDA) using the 510(k) process including the collagen cross-links tests; pyrilinks test from Metra Biosystems which measures collagen type 1 cross-link, pyridium, Osteomark test from Ostex International which measures cross-linked N-telopeptides of type 1 collagen (NTx), and Serum Crosslaps One-step ELISA test which measures hydroxyproline. Other bone turnover cleared through the FDA 510(k) process tests include; Ostase from Beckman Coulter which measures bone-specific alkaline phosphatase (B-ALP), N-MID Osteocalcin One-step ELISA from Osteometer Bio Tech which measures osteocalcin (OC), and Elecsys® N-MID Osteocalcin Immunoassay (Roche Diagnostics).

Other tests of bone turnover are considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories. LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared these tests; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

National Osteoporosis Foundation
In 2014, the National Osteoporosis Foundation updated their guideline for prevention and treatment of osteoporosis (Cosman et al., 2014). 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)

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

International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)
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 (Vasikaran, Cooper, et al., 2011). 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
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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 and the International Osteoporosis Foundation (IOF)**
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.” (Hans et al., 2011)

**American Association of Clinical Endocrinologists and American College of Endocrinology**
The 2016 AACE/ACE guidelines (Camacho et al., 2016) recommend:

“Consider using bone turnover markers (BTMs) 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 B; BEL 1,downgraded based on expert consensus).”

“Consider using BTMs for assessing patient compliance and therapy efficacy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction; significant increases indicate good response to anabolic therapy (Grade B; BEL 1; downgraded based on expert consensus).”

They summarize that BTMs provide a dynamic and useful assessment of skeletal activity, however their use in clinical practice is limited by high assay variability, poor individual predictive ability and lack of evidence-based thresholds for clinical decision making.

**U.S. Preventative Services Task Force**
The U.S. Preventative Services Task Force (USPSTF) 2018 recommendation on screening to prevent osteoporotic fractures (Viswanathan et al., 2018) address clinical risk assessment and bone density measurement but do not mention bone turnover markers.

**Billing/Coding/Physician Documentation Information**
This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes:* 82523, 83500, 83505, 83937, 84080

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**

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handling and patient preparation to reduce pre-analytical variability. Osteoporos Int, 28(9), 2541-2556. doi:10.1007/s00198-017-4082-4


Policy Implementation/Update Information

1/1/19 New policy developed. Measurement of bone turnover markers is considered investigational for the diagnosis and management of osteoporosis and in the management of patients with conditions associated with high rates of bone turnover. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)

10/1/19 Policy statement revised to read; The measurement of bone turnover markers for the diagnosis and management of osteoporosis and in the management of patients with conditions associated with high rates of bone turnover is not covered. Wording revised in the Not Covered section. “Investigational” changed to read “Reimbursement is not allowed…” Deleted coding grid. Notification given 10/1/2019 for policy effective date 12/2/2019. (an)

12/10/19 Policy title changed from “Bone Turnover Markers for Diagnosis and Management of Osteoporosis and Diseases Associated with High Bone Turnover” to “Bone Turnover Markers Testing”. Coding section updated to reflect new codes per Avalon Q3 CAB update. Note 1 added to When not covered section for clarity. (eel)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.