

Corporate Medical Policy

Bone Turnover Markers Testing AHS – G2051

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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, 2019b).

Bone formation markers:

- Serum bone-specific alkaline phosphatase (BSAP/BALP)
- Serum osteocalcin (OC)
- Serum type 1 procollagen (C-terminal/N-terminal): C1NP or P1NP

Bone resorption markers:

- Urinary hydroxyproline (HYP)
- 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

Not applicable.

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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 diagnosis and management of patients with other 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, 2019a, 2019b; Talwar, 2017):

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

2. Bone resorption markers:
 - a. Urinary hydroxyproline (HYP)
 - 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

The resorption and reformation of bone are normally tightly regulated and coupled so that bone mass does not change. Bone disease occurs when these processes are uncoupled (Rosen, 2018, 2019a). Biomarkers involved in the processes of resorption or formation have been proposed as measures for prediction of future bone loss, fracture risk, and more. Resorption markers include pyridinium crosslinks (PYD, DPD), C- and N-telopeptides (CTX, ICTP, NTX), tartrate-resistant acid phosphatase (TRACP) 5b, and cathepsin K, while formation markers include procollagen type I propeptides (PICP, PINP), osteocalcin, and bone-specific alkaline phosphatase (BSAP, also known as BALP) (Rosen, 2018, 2019a).

Formation markers are characteristic of bone formation rate. PICP and PINP are carboxy- and amino-sides of the tropocollagen peptide, which is a precursor to type I collagen in bone. The serum concentration of these peptides reflects synthesis of new collagen. Osteocalcin is a component of osteoid, and BSAP is the alkaline phosphatase specific to osteoblasts. These biomarkers reflect the activity of osteoblasts. Of these markers, BSAP and PINP are considered the most clinically useful (Rosen, 2019a, 2019b).

Resorption markers are characteristic of bone resorption rate (breakdown of bone). Pyridinium crosslinks are components of bone collagen, C- and N- telopeptides are crosslinks between bone collagen molecules, TRACP is anchored to the osteoclasts that initiate bone resorption, and cathepsin K is involved in digestion of the organic matrix (Manolagas, 2018; Rosen, 2017, 2019b). Of these markers, urinary NTX and serum CTX are considered the most clinically useful (Rosen, 2017, 2019b).

The measurement and use of these biomarkers remain complicated. Biologic variability between and within patients is significant, as factors such as age, gender, body mass index, circadian rhythms,

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menstruation, smoking, time of food consumption, exercise, and more may influence the levels of BTMs (Rosen, 2017, 2018, 2019a, 2019b). Moreover, assays used to measure these biomarkers vary considerably, as both urinary and serum samples have been used. Lack of standardization has limited the use of BTMs in the clinical setting (Rosen, 2017, 2019b).

Analytical Validity

Eastell et al. assessed the biological variability between serum and urinary N-telopeptides of type I collagen (NTX). 277 postmenopausal women were included, and urine and serum specimens were included to identify short-term variability. Long-term variability was determined by comparing NTX at baseline and at 2 months. The authors found the median short-term coefficient of variation (CV) was 13.1% for urinary NTX and 6.3% for serum NTX. Long-term CV% was found to be 15.6% for urinary NTX and 7.5% for serum NTX. The authors also observed that to be 90% confident that a decrease in NTX after antiresorptive therapy was not caused by variability alone, a 31% decrease in urinary NTX and a 14% decrease in serum NTX are needed (R. Eastell et al., 2000).

Seibel et al. (2001) described the results of an international proficiency testing program for biochemical bone markers among clinical laboratories. The authors sent out 2 urinary and 2 serum pools (both normal and increased concentrations of markers) to 79 laboratories. The CVs were as follows: “serum bone-specific alkaline phosphatase (n = 47 laboratories), 16–48%; serum osteocalcin (n = 31), 16–42%; urinary free deoxypyridinoline (n = 30), 6.4–12%; urinary total deoxypyridinoline and pyridinoline (n = 29), 27–28%; urinary N-terminal cross-linked telopeptide of type I collagen (n = 10), 39%; serum C-terminal cross-linked telopeptide of type I collagen (ICTP; n = 8), 22–27%; urinary hydroxyproline (n = 13), 12%”. The authors concluded that “even with identical assays and methods, results for most biochemical markers of bone turnover differ markedly among laboratories (Seibel et al., 2001).”

Schafer et al. (2010) assessed the laboratory reproducibility of urine N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP). The authors obtained serum and urine from five postmenopausal women and sent specimens to six labs over 8 months. They 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.”

Hlaing et al. notes that “although automated platforms have substantially improved the analytical variability of bone turnover markers, reproducibility still varies substantially” (Hlaing & Compston, 2014). 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 such as CTx and PINP are ongoing (IFCC, 2018).

Clinical Validity and Utility

Johansson et al. (2014) performed a meta-analysis 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.” Six studies were included. The authors identified a “significant” association between s-CTX and risk of fracture (gradient of risk [GR] = 1.18). The hazard ratio per standard deviation increase in s-PINP was found to be 1.23 for men and women and unadjusted for bone mineral density. The association between s-CTX and fracture risk was found to be 1.23. The authors concluded that “there is a modest but significant association between BTMs and risk of future fractures”.

Marques et al. “assessed whether circulating bone formation and resorption markers (BTM) were individual predictors for trabecular and cortical bone loss, periosteal expansion, and fracture risk in older adults aged 66 to 93”. 1069 participants were included. Bone formation was assessed by serum

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procollagen type I N propeptide (PINP) and osteocalcin, and bone resorption was assessed by C-terminal cross-linking telopeptide of type I collagen (CTX). Inter-assay coefficients of variation were <3% for all BTM. A total of 54 men and 182 women sustained a fracture during the median follow-up of 11.7 years. The authors found that “increase in BTM levels was associated with faster cortical and trabecular bone loss at the femoral neck and proximal femur in men and women. Higher BTM levels were positively related with periosteal expansion rate at the femoral neck in men. Markers were not associated with fracture risk (Marques et al., 2016).”

Mederle et al. investigated the correlation between bone mass density (BMD) and “serum levels of BTMs (tartrate-resistant acid phosphatase-5b [TRAP-5b]), bone-specific alkaline phosphatase (BSAP), in postmenopausal osteoporotic women as compared to healthy postmenopausal subjects”. 132 postmenopausal women with osteoporosis were included along with 81 healthy postmenopausal women. BSAP was found to have a sensitivity of 76.5% and specificity of 84.3% at a cutoff of 21.27 U/L, and TRAP-5b was found to have a sensitivity of 86.3% and specificity of 90.6% at a cutoff of 3.45 U/L. The authors concluded that “our study showed that BMD correlates negatively with BTMs and TRAP-5b presents a good specificity in identifying patients with postmenopausal osteoporosis (Mederle et al., 2018).”

Tian et al. performed a meta-analysis “to explore whether bone turnover biomarkers (BTMs), i.e., C-terminal telopeptide of type I collagen (CTX) and procollagen type I aminoterminal propeptide (PINP), are associated with fracture.” Nine studies were included. PINP had a “significant” positive association with fracture (adjusted gradient risk [GR] = 1.28) after adjusting for confounders. CTX was also seen to associate with fracture (GR = 1.20). The authors concluded, “Our results indicate a statistically significant but modest association between BTMs (s-PINP or s-CTX) and future fracture risk after adjusting for BMD and clinical risk factors. The causal relationship between the two clinical conditions requires future validation with more standardized studies (Tian et al., 2019).”

Naylor et al. evaluated bone turnover markers (BTMs)’ ability to monitor “offset of treatment with bisphosphonates (BP) in osteoporosis”. This was done by comparing the changes in BTMs and total hip (TH) bone mineral density (BMD). CTX and PINP were the BTMs analyzed, and offset was defined by “an increase greater than the least significant change (LSC) and an increase above the reference mean value”. Fifty women were included, and at 48 weeks after stopping BPs, “CTX was greater than the LSC for 66% of women and PINP 72%; CTX was above the reference mean for 64% of women and PINP 42%”. The authors also found that the decrease in TH-BMD was greater for women with the largest increases in BTMs, compared to those with “continued suppression”. The authors concluded that “The measurement of BTM after withdrawal of BPs is potentially useful to evaluate patients that are taking a pause from treatment. An increase in BTMs more than the LSC and/or reference mean reflects loss of treatment effect and identifies patients that are likely to have a decrease in BMD” (Naylor et al., 2019).

Massera et al. evaluated the associations of osteocalcin (OC) and C-telopeptide of type I collagen (CTX) with “long-term incidence of hip fracture in older women”. 1680 women from the population-based Cardiovascular Health Study were included, and over a median follow-up period of 12.3 years, 288 hip fractures occurred. The authors found that increasing levels of CTX up to the middle-upper range (hazard ratio = 1.52 per standard deviation increase), with increases past this range only incrementally increasing risk (hazard ratio = 0.8). The authors identified an “inverted U-shaped relationship with incident fracture after adjustment” when comparing quartiles to each other, and an association was only seen for the quartile 3 to quartile 1 comparison (hazard ratio = 1.63). In a subset with “available measures”, both OC and CTX were “inversely associated with bone mineral density of the hip”. The authors concluded that “CTX, but not OC, levels were associated with incident hip fracture in post-menopausal women, a relationship characterized by an inverted U-shape” (Massera et al., 2019).

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

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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 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.”

American Association of Clinical Endocrinologists and American College of Endocrinology (P. M. Camacho et al., 2016; Pauline M. Camacho et al., 2020)

An update to the 2016 Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis was published in 2020. In it, the AACE/ACE state “Consider using bone turnover markers in the

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initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk”, which is identical to the 2016 statement, but the 2020 edition is graded at an “A”, up from “B” in 2016.

Similarly, the statement “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” remains unchanged from the 2016 version.

Other relevant recommendations include:

- “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.”
- “The ending of a bisphosphonate holiday should be based on individual patient circumstances such as... an increase in bone turnover markers.”

Overall, although the joint guidelines acknowledge that BTMs cannot diagnose osteoporosis, they note that “elevated levels can predict more rapid rates of bone loss” and “are associated with increased fracture risk independent of BMD [bone mineral density] in some studies”. Further, automated immunoassays have improved BTMs’ reproducibility, and “changes in markers have been associated with bone response to therapy and reduction of fracture risk”. Despite the numerous analytical issues with BTM assessment (lack of standardization, high cost, et al.), the guidelines note that some experts routinely use BTMs in clinical practice. They also note that the preferred bone turnover markers are PINP for bone formation and CTX for bone resorption. And, in the situations when patients might experience renal insufficiency or when there are insurance issues, then bone-specific alkaline phosphatase may be used. The guidelines conclude that “BTMs are useful in certain situations, such as assessment of fracture risk and to provide early feedback to patients that their drug is or is not working, which leads to discussions pertaining to medication compliance, drug absorption, and/or therapeutic efficacy. BTMs do not need to be assessed in all osteoporosis patients” (Pauline M. Camacho et al., 2020).

Consensus Group Report, managed by Scientific Advisory Board of European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (Lorentzon et al., 2019)

This working group was intended to “to provide guidance to clinicians on how to use BTMs in patient evaluation in postmenopausal osteoporosis, in fracture risk prediction and in the monitoring of treatment efficacy and adherence to osteoporosis medication”. Their conclusions are listed below:

- “The bone formation marker serum PINP [N-terminal collagen type I extension propeptide] and resorption marker serum β CTX-I [bone alkaline phosphatase for bone formation and C-terminal cross-linking telopeptide of type I collagen] are the preferred markers for evaluating bone turnover in the clinical setting.”
- “Bone turnover markers cannot be used to diagnose osteoporosis but can be of value in patient evaluation and can improve the ability to detect some causes of secondary osteoporosis.”
- “Serum β CTX-I and PINP correlate only moderately with bone loss in postmenopausal women and with osteoporosis medication-induced gains in BMD. Therefore, the use of bone turnover markers cannot be recommended to monitor osteoporosis treatment effect in individual patients.”

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- “Adding data on serum β CTX-I and PINP levels in postmenopausal women can only improve fracture risk prediction slightly in addition to clinical risk factors and BMD and therefore has limited value.”
- “Bisphosphonates are the most commonly used osteoporosis medications, but adherence to oral bisphosphonates falls below 50% within the first year of treatment. Monitoring PINP and β CTX-I is effective in monitoring treatment adherence and can be defined as the sufficient suppression of these markers (by more than the LSC or to the lower half of the reference interval for young and healthy premenopausal women)”.

The guideline remarks “It is possible that monitoring the bone marker response may aid in the use of bisphosphonate treatment frequency and dosing when denosumab treatment is stopped.” (Lorentzon et al., 2019)

U.S. Preventative Services Task Force (USPSTF) (Viswanathan et al., 2018)

The 2018 USPSTF 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.

Endocrine Society (Richard Eastell et al., 2019; Shoback et al., 2020; Singer et al., 2014)

The Endocrine Society released a guideline titled “*Pharmacological Management of Osteoporosis in Postmenopausal Women*”, which noted, “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 (Richard Eastell et al., 2019).”

The Endocrine Society published an update to the above guideline in 2020, and the above statement concerning monitoring of bone turnover markers remained in the 2020 edition (Shoback et al., 2020). The Endocrine Society also released guidelines regarding the management of Paget’s Disease. They recommended “that in patients with increased bone turnover, biochemical follow-up should be used as a more objective indicator of relapse than symptoms” (Singer et al., 2014).

“For most patients, measurement of total alkaline phosphatase or other baseline disease activity markers at 6 to 12 weeks, when bone turnover will have shown a substantial decline, is an acceptable and cost-effective option” (Singer et al., 2014).

National Osteoporosis Guideline Group (NOGG, 2017)

The NOGG notes bone turnover markers as a possible measure to evaluate during investigation of osteoporosis (NOGG, 2017).

Kidney Disease Improving Global Outcomes (KDIGO): Mineral and bone disorder (KDIGO, 2017)

KDIGO released guidelines pertaining to bone turnover related to CKD.

- “In patients with CKD [stages] G3a–G5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover.”
- “In patients with CKD [stages] G3a–G5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline)” (KDIGO, 2017).

The **Renal Association** also published a “commentary” on the KDIGO guidelines in 2018. In it, they remarked that “Although iPTH, whole PTH, and bALP levels were associated with bone turnover, no

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biomarker singly or in combination was sufficiently robust to diagnose low, normal, and high bone turnover in an individual patient [on dialysis].” (Burton, Goldsmith, Ruddock, Shroff, & Wan, 2018)

Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (Bilezikian et al., 2014)

This workshop published guidelines regarding management of asymptomatic primary hyperparathyroidism (PHPT). They note bone turnover markers as an optional measurement of asymptomatic PHPT, listing “bone-specific alkaline phosphatase activity, osteocalcin, P1NP [select one]; serum CTX, urinary NTX [select one]” (Bilezikian et al., 2014).

International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (Kanis, Cooper, Rizzoli, & Reginster, 2018)

The IOF/ESCEO issued joint guidelines stating the following:

“Bone markers (serum procollagen type I N propeptide (s-P1NP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) as markers of bone formation and bone resorption, respectively) have some prognostic significance for fracture in situations where bone mineral density (BMD) is unavailable.”

The joint guidelines also note that if harmonization efforts for other bone turnover markers are successful, these markers may see use for fracture risk. Procollagen I N-terminal peptide (P1NP) and C-telopeptide breakdown products (especially serum CTX) are considered the most informative biochemical markers for monitoring of osteoporosis (Kanis et al., 2018).

The International Federation of Clinical Chemistry and Laboratory Medicine (Bhattoa, 2018)

The most recent review of bone turnover markers for the journal of the International Federation of Clinical Chemistry and Laboratory Medicine (Bhattoa, 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 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.”

International Society for Clinical Densitometry (ISCD, 2019)

The ISCD includes a comment on bone turnover markers in their guideline titled “Official Positions”, stating that “Serial BMD [bone mineral density] testing in combination with clinical assessment of fracture risk, bone turnover markers and other factors...can be used to determine whether treatment should be initiated in untreated patients, according to locally applicable guidelines” (ISCD, 2019).

Paget's Association, Guideline Development Group (Ralston et al., 2019)

This Guideline Development Group published a guideline titled “Diagnosis and Management of Paget's Disease of Bone in Adults”. The relevant remarks include:

- “Serum total ALP [total alkaline phosphatase] is widely available and considerably cheaper than other biochemical markers that have been assessed in PDB [Paget's Disease of Bone].”
- “If total ALP values are normal and clinical suspicion of metabolically active PDB is high, measurement of BALP, PINP, or uNTX may be considered to screen for metabolically active disease.”
- “...elevations in markers of bone turnover occur in many disease states and cannot be used in isolation for the diagnosis of PDB.”

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- “Measurement of PINP is recommended to predict lesion extent, as defined by scintigraphy, after bisphosphonate therapy.”
- “Measurement of biochemical markers of bone turnover are not recommended a means of predicting the response of bone pain to osteoclast inhibitors in PDB” (Ralston et al., 2019).

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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Specialty Matched Consultant Advisory Panel 9/2020

Policy Implementation/Update Information

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| 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) |
| 10/13/20 | Specialty Matched Consultant Advisory Panel review 9/29/20. No change to policy statement. (eel) |
| 11/10/20 | Reviewed by Avalon 3 rd quarter CAB. Background, policy guidelines, and references updated. Related Policies section added. Medical Director review 10/2020. (bb) |

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

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and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.