National Coverage Determination
Procedure Code: 82523
Collagen Crosslinks, Any Method
CMS Policy Number: 190.19
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Description: Collagen crosslinks, part of the matrix of bone upon which bone mineral is deposited, are biochemical markers the excretion of which provides a quantitative measurement of bone resorption. Elevated levels of urinary collagen crosslinks indicate elevated bone resorption. Elevated bone resorption contributes to age-related and postmenopausal loss of bone leading to osteoporosis and increased risk of fracture. The collagen crosslinks assay can be performed by immunoassay or by high performance liquid chromatography (HPLC). Collagen crosslink immunoassays measure the pyridinoline crosslinks and associated telopeptides in urine.

Bone is constantly undergoing a metabolic process called turnover or remodeling. This includes a degradation process, bone resorption, mediated by the action of osteoclasts, and a building process, bone formation, mediated by the action of osteoblasts. Remodeling is required for the maintenance and overall health of bone and is tightly coupled; that is, resorption and formation must be in balance. In abnormal states of bone remodeling, when resorption exceeds formation, it results in a net loss of bone. The measurement of specific, bone-derived resorption products provides analytical data about the rate of bone resorption.

Osteoporosis is a condition characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures of the hip, spine, and wrist. The term primary osteoporosis is applied where the causal factor in the disease is menopause or aging. The term secondary osteoporosis is applied where the causal factor is something other than menopause or aging, such as long-term administration of glucocorticosteroids, endocrine-related disorders (other than loss of estrogen due to menopause), and certain bone diseases such as cancer of the bone.

With respect to quantifying bone resorption, collagen crosslink tests can provide adjunct diagnostic information in concert with bone mass measurements. Bone mass measurements and biochemical markers may have complementary roles to play in assessing effectiveness of osteoporosis treatment. Proper management of osteoporosis patients, who are on long-term therapeutic regimens, may include laboratory testing of biochemical markers of bone turnover, such as collagen crosslinks, that provide a profile of bone turnover responses within weeks of therapy. Changes in collagen

crosslinks are determined following commencement of antiresorptive therapy. These can be measured over a shorter time interval when compared to bone mass density. If bone resorption is not elevated, repeat testing is not medically necessary.

Indications:
Generally speaking, collagen crosslink testing is useful mostly in "fast losers" of bone. The age when these bone markers can help direct therapy is often pre-Medicare. By the time a fast loser of bone reaches age 65, she will most likely have been stabilized by appropriate therapy or have lost so much bone mass that further testing is useless. Coverage for bone marker assays may be established, however, for younger Medicare beneficiaries and for those men and women who might become fast losers because of some other therapy such as glucocorticoids. Safeguards should be incorporated to prevent excessive use of tests in patients for whom they have no clinical relevance.

Collagen crosslinks testing is used to:

- Identify individuals with elevated bone resorption, who have osteoporosis in whom response to treatment is being monitored.
- Predict response (as assessed by bone mass measurements) to FDA approved antiresorptive therapy in postmenopausal women.
- Assess response to treatment of patients with osteoporosis, Paget's disease of the bone, or risk for osteoporosis where treatment may include FDA approved antiresorptive agents, anti- estrogens or selective estrogen receptor moderators.

Limitations:
Because of significant specimen to specimen collagen crosslink physiologic variability (15-20%), current recommendations for appropriate utilization include: one or two base-line assays from specified urine collections on separate days; followed by a repeat assay about 3 months after starting anti-resorptive therapy; followed by a repeat assay in 12 months after the 3-month assay; and thereafter not more than annually, unless there is a change in therapy in which circumstance an additional test may be indicated 3 months after the initiation of new therapy.

Some collagen crosslink assays may not be appropriate for use in some disorders, according to FDA labeling restrictions.

Frequency Limitations: Current recommendations for appropriate utilization include: one or two base-line assays from specified urine collections on separate days; followed by a repeat assay about three months after starting anti-resorptive therapy; followed by a repeat assay in 12 months after the three-month assay; and thereafter

not more than annually, unless there is a change in therapy in which circumstance an additional test may be indicated three months after the initiation of new therapy.

To review all requirements of this policy, please see: CMS NCD listing by Chapter

Covered ICD-10 Codes.

ICD-10	Descriptor
C44.1321	Sebaceous cell carcinoma skin/ r upper eyelid, inc canthus
C44.1322	Sebaceous cell carcinoma skin/ right low eyelid, inc canthus
C44.1391	Sebaceous cell carcinoma skin/ left upr eyelid, inc canthus
C44.1392	Sebaceous cell carcinoma skin/ left low eyelid, inc canthus
E05.00	Thyrotoxicosis w diffuse goiter w/o thyrotoxic crisis
E05.01	Thyrotoxicosis w diffuse goiter w thyrotoxic crisis or storm
E05.10	Thyrotxcosis w toxic sing thyroid nodule w/o thyrotxc crisis
E05.11	Thyrotxcosis w toxic single thyroid nodule w thyrotxc crisis
E05.20	Thyrotxcosis w toxic multinod goiter w/o thyrotoxic crisis
E05.21	Thyrotxcosis w toxic multinodular goiter w thyrotoxic crisis
E05.30	Thyrotxcosis from ectopic thyroid tissue w/o thyrotxc crisis
E05.31	Thyrotxcosis from ectopic thyroid tissue w thyrotoxic crisis
E05.40	Thyrotoxicosis factitia without thyrotoxic crisis or storm
E05.41	Thyrotoxicosis factitia with thyrotoxic crisis or storm
E05.80	Other thyrotoxicosis without thyrotoxic crisis or storm
E05.81	Other thyrotoxicosis with thyrotoxic crisis or storm
E05.90	Thyrotoxicosis, unsp without thyrotoxic crisis or storm
E05.91	Thyrotoxicosis, unspecified with thyrotoxic crisis or storm
E06.3	Autoimmune thyroiditis
E07.9	Disorder of thyroid, unspecified
E21.0	Primary hyperparathyroidism
E21.1	Secondary hyperparathyroidism, not elsewhere classified
E21.2	Other hyperparathyroidism
E21.3	Hyperparathyroidism, unspecified
E28.310	Symptomatic premature menopause
E28.319	Asymptomatic premature menopause
E28.39	Other primary ovarian failure
E28.8	Other ovarian dysfunction
E28.9	Ovarian dysfunction, unspecified
E55.9	Vitamin D deficiency, unspecified
E58	Dietary calcium deficiency
E59	Dietary selenium deficiency

E60	Dietary zinc deficiency
E61.0	Copper deficiency
E61.1	Iron deficiency
E61.2	Magnesium deficiency
E61.3	Manganese deficiency
E61.4	Chromium deficiency
E61.5	Molybdenum deficiency
E61.6	Vanadium deficiency
E88.02	Plasminogen deficiency
E89.40	Asymptomatic postprocedural ovarian failure
E89.41	Symptomatic postprocedural ovarian failure
M48.50XA	Collapsed vertebra, NEC, site unsp, init
M48.51XA	Collapsed vertebra, NEC, occipito-atlanto-axial region, init
M48.52XA	Collapsed vertebra, NEC, cervical region, init
M48.53XA	Collapsed vertebra, NEC, cervicothoracic region, init
M48.54XA	Collapsed vertebra, NEC, thoracic region, init
M48.55XA	Collapsed vertebra, NEC, thoracolumbar region, init
M48.56XA	Collapsed vertebra, NEC, lumbar region, init
M48.57XA	Collapsed vertebra, NEC, lumbosacral region, init
M48.58XA	Collapsed vertebra, NEC, sacr/sacrocygl region, init
M80.00XA	Age-rel osteopor w current path fracture, unsp site, init
M80.011A	Age-rel osteopor w current path fracture, r shoulder, init
M80.012A	Age-rel osteopor w current path fracture, l shoulder, init
M80.019A	Age-rel osteopor w current path fx, unsp shoulder, init
M80.021A	Age-rel osteopor w current path fracture, r humerus, init
M80.022A	Age-rel osteopor w current path fracture, l humerus, init
M80.029A	Age-rel osteopor w current path fracture, unsp humerus, init
M80.031A	Age-rel osteopor w current path fracture, r forearm, init
M80.032A	Age-rel osteopor w current path fracture, l forearm, init
M80.039A	Age-rel osteopor w current path fracture, unsp forearm, init
M80.041A	Age-rel osteopor w current path fracture, right hand, init
M80.042A	Age-rel osteopor w current path fracture, left hand, init
M80.049A	Age-rel osteopor w current path fracture, unsp hand, init
M80.051A	Age-rel osteopor w current path fracture, right femur, init
M80.052A	Age-rel osteopor w current path fracture, left femur, init
M80.059A	Age-rel osteopor w current path fracture, unsp femur, init
M80.061A	Age-rel osteopor w current path fracture, r low leg, init
M80.062A	Age-rel osteopor w current path fracture, l low leg, init
M80.069A	Age-rel osteopor w current path fracture, unsp low leg, init
M80.071A	Age-rel osteopor w current path fracture, right ank/ft, init
M80.072A	Age-rel osteopor w current path fracture, left ank/ft, init
M80.079A	Age-rel osteopor w current path fracture, unsp ank/ft, init

M80.08XA	Age-rel osteopor w current path fracture, vertebra(e), init
M80.80XA	Oth osteopor w current path fracture, unsp site, init
M80.811A	Oth osteopor w current path fracture, r shoulder, init
M80.812A	Oth osteopor w current path fracture, l shoulder, init
M80.819A	Oth osteopor w current path fracture, unsp shoulder, init
M80.821A	Oth osteopor w current path fracture, r humerus, init
M80.822A	Oth osteopor w current path fracture, l humerus, init
M80.829A	Oth osteopor w current path fracture, unsp humerus, init
M80.831A	Oth osteopor w current path fracture, r forearm, init
M80.832A	Oth osteopor w current path fracture, l forearm, init
M80.839A	Oth osteopor w current path fracture, unsp forearm, init
M80.841A	Oth osteopor w current path fracture, right hand, init
M80.842A	Oth osteopor w current path fracture, left hand, init
M80.849A	Oth osteopor w current path fracture, unsp hand, init
M80.851A	Oth osteopor w current path fracture, right femur, init
M80.852A	Oth osteopor w current path fracture, left femur, init
M80.859A	Oth osteopor w current path fracture, unsp femur, init
M80.861A	Oth osteopor w current path fracture, r low leg, init
M80.862A	Oth osteopor w current path fracture, l low leg, init
M80.869A	Oth osteopor w current path fracture, unsp lower leg, init
M80.871A	Oth osteopor w current path fracture, right ank/ft, init
M80.872A	Oth osteopor w current path fracture, left ank/ft, init
M80.879A	Oth osteopor w current path fracture, unsp ank/ft, init
M80.88XA	Oth osteopor w current path fracture, vertebra(e), init
M81.0	Age-related osteoporosis w/o current pathological fracture
M81.6	Localized osteoporosis [Lequesne]
M81.8	Other osteoporosis without current pathological fracture
M84.40XA	Pathological fracture, unsp site, init encntr for fracture
M84.411A	Pathological fracture, right shoulder, init for fx
M84.412A	Pathological fracture, left shoulder, init for fx
M84.419A	Pathological fracture, unsp shoulder, init for fx
M84.421A	Pathological fracture, right humerus, init for fx
M84.422A	Pathological fracture, left humerus, init for fx
M84.429A	Pathological fracture, unsp humerus, init for fx
M84.431A	Pathological fracture, right ulna, init encntr for fracture
M84.432A	Pathological fracture, left ulna, init encntr for fracture
M84.433A	Pathological fracture, right radius, init for fx
M84.434A	Pathological fracture, left radius, init encntr for fracture
M84.439A	Pathological fracture, unsp ulna and radius, init for fx
M84.441A	Pathological fracture, right hand, init encntr for fracture
M84.442A	Pathological fracture, left hand, init encntr for fracture
M84.443A	Pathological fracture, unsp hand, init encntr for fracture

M84.444A	Pathological fracture, right finger(s), init for fx
M84.445A	Pathological fracture, left finger(s), init for fx
M84.446A	Pathological fracture, unsp finger(s), init for fx
M84.451A	Pathological fracture, right femur, init encntr for fracture
M84.452A	Pathological fracture, left femur, init encntr for fracture
M84.453A	Pathological fracture, unsp femur, init encntr for fracture
M84.454A	Pathological fracture, pelvis, init encntr for fracture
M84.459A	Pathological fracture, hip, unsp, init encntr for fracture
M84.461A	Pathological fracture, right tibia, init encntr for fracture
M84.462A	Pathological fracture, left tibia, init encntr for fracture
M84.463A	Pathological fracture, right fibula, init for fx
M84.464A	Pathological fracture, left fibula, init encntr for fracture
M84.469A	Pathological fracture, unsp tibia and fibula, init for fx
M84.471A	Pathological fracture, right ankle, init encntr for fracture
M84.472A	Pathological fracture, left ankle, init encntr for fracture
M84.473A	Pathological fracture, unsp ankle, init encntr for fracture
M84.474A	Pathological fracture, right foot, init encntr for fracture
M84.475A	Pathological fracture, left foot, init encntr for fracture
M84.476A	Pathological fracture, unsp foot, init encntr for fracture
M84.477A	Pathological fracture, right toe(s), init for fx
M84.478A	Pathological fracture, left toe(s), init encntr for fracture
M84.479A	Pathological fracture, unsp toe(s), init encntr for fracture
M84.48XA	Pathological fracture, other site, init encntr for fracture
M84.50XA	Pathological fracture in neoplastic disease, unsp site, init
M84.511A	Path fracture in neoplastic disease, r shoulder, init
M84.512A	Path fracture in neoplastic disease, l shoulder, init
M84.519A	Path fracture in neoplastic disease, unsp shoulder, init
M84.521A	Pathological fracture in neoplastic disease, r humerus, init
M84.522A	Pathological fracture in neoplastic disease, l humerus, init
M84.529A	Path fracture in neoplastic disease, unsp humerus, init
M84.531A	Path fracture in neoplastic disease, right ulna, init
M84.532A	Pathological fracture in neoplastic disease, left ulna, init
M84.533A	Path fracture in neoplastic disease, right radius, init
M84.534A	Path fracture in neoplastic disease, left radius, init
M84.539A	Path fracture in neopltc disease, unsp ulna and radius, init
M84.541A	Path fracture in neoplastic disease, right hand, init
M84.542A	Pathological fracture in neoplastic disease, left hand, init
M84.549A	Pathological fracture in neoplastic disease, unsp hand, init
M84.550A	Pathological fracture in neoplastic disease, pelvis, init
M84.551A	Path fracture in neoplastic disease, right femur, init
M84.552A	Path fracture in neoplastic disease, left femur, init
M84.553A	Path fracture in neoplastic disease, unsp femur, init

M84.559A	Pathological fracture in neoplastic disease, hip, unsp, init
M84.561A	Path fracture in neoplastic disease, right tibia, init
M84.562A	Path fracture in neoplastic disease, left tibia, init
M84.563A	Path fracture in neoplastic disease, right fibula, init
M84.564A	Path fracture in neoplastic disease, left fibula, init
M84.569A	Path fx in neopltc disease, unsp tibia and fibula, init
M84.571A	Path fracture in neoplastic disease, right ankle, init
M84.572A	Path fracture in neoplastic disease, left ankle, init
M84.573A	Path fracture in neoplastic disease, unsp ankle, init
M84.574A	Path fracture in neoplastic disease, right foot, init
M84.575A	Pathological fracture in neoplastic disease, left foot, init
M84.576A	Pathological fracture in neoplastic disease, unsp foot, init
M84.58XA	Pathological fracture in neoplastic disease, oth site, init
M84.60XA	Pathological fracture in oth disease, unsp site, init for fx
M84.611A	Pathological fracture in oth disease, right shoulder, init
M84.612A	Pathological fracture in oth disease, left shoulder, init
M84.619A	Pathological fracture in oth disease, unsp shoulder, init
M84.621A	Pathological fracture in oth disease, right humerus, init
M84.622A	Pathological fracture in oth disease, left humerus, init
M84.629A	Pathological fracture in oth disease, unsp humerus, init
M84.631A	Pathological fracture in oth disease, right ulna, init
M84.632A	Pathological fracture in oth disease, left ulna, init for fx
M84.633A	Pathological fracture in oth disease, right radius, init
M84.634A	Pathological fracture in oth disease, left radius, init
M84.639A	Path fracture in oth disease, unsp ulna and radius, init
M84.641A	Pathological fracture in oth disease, right hand, init
M84.642A	Pathological fracture in oth disease, left hand, init for fx
M84.649A	Pathological fracture in oth disease, unsp hand, init for fx
M84.650A	Pathological fracture in oth disease, pelvis, init for fx
M84.651A	Pathological fracture in oth disease, right femur, init
M84.652A	Pathological fracture in oth disease, left femur, init
M84.653A	Pathological fracture in oth disease, unsp femur, init
M84.659A	Pathological fracture in oth disease, hip, unsp, init for fx
M84.661A	Pathological fracture in oth disease, right tibia, init
M84.662A	Pathological fracture in oth disease, left tibia, init
M84.663A	Pathological fracture in oth disease, right fibula, init
M84.664A	Pathological fracture in oth disease, left fibula, init
M84.669A	Path fracture in oth disease, unsp tibia and fibula, init
M84.671A	Pathological fracture in oth disease, right ankle, init
M84.672A	Pathological fracture in oth disease, left ankle, init
M84.673A	Pathological fracture in oth disease, unsp ankle, init
M84.674A	Pathological fracture in oth disease, right foot, init

M84.675A	Pathological fracture in oth disease, left foot, init for fx
M84.676A	Pathological fracture in oth disease, unsp foot, init for fx
M84.68XA	Pathological fracture in oth disease, oth site, init for fx
M84.751A	Incomplete atypical femoral fracture, right leg, init
M85.80	Oth disrd of bone density and structure, unspecified site
M85.811	Oth disrd of bone density and structure, right shoulder
M85.812	Oth disrd of bone density and structure, left shoulder
M85.819	Oth disrd of bone density and structure, unsp shoulder
M85.821	Oth disrd of bone density and structure, right upper arm
M85.822	Oth disrd of bone density and structure, left upper arm
M85.829	Oth disrd of bone density and structure, unsp upper arm
M85.831	Oth disrd of bone density and structure, right forearm
M85.832	Oth disrd of bone density and structure, left forearm
M85.839	Oth disrd of bone density and structure, unspecified forearm
M85.841	Oth disrd of bone density and structure, right hand
M85.842	Oth disrd of bone density and structure, left hand
M85.849	Oth disrd of bone density and structure, unspecified hand
M85.851	Oth disrd of bone density and structure, right thigh
M85.852	Oth disrd of bone density and structure, left thigh
M85.859	Oth disrd of bone density and structure, unspecified thigh
M85.861	Oth disrd of bone density and structure, right lower leg
M85.862	Oth disrd of bone density and structure, left lower leg
M85.869	Oth disrd of bone density and structure, unsp lower leg
M85.871	Oth disrd of bone density and structure, right ank/ft
M85.872	Oth disrd of bone density and structure, left ankle and foot
M85.879	Oth disrd of bone density and structure, unsp ankle and foot
M85.88	Oth disrd of bone density and structure, other site
M85.89	Oth disrd of bone density and structure, multiple sites
M85.9	Disorder of bone density and structure, unspecified
M88.0	Osteitis deformans of skull
M88.1	Osteitis deformans of vertebrae
M88.811	Osteitis deformans of right shoulder
M88.812	Osteitis deformans of left shoulder
M88.819	Osteitis deformans of unspecified shoulder
M88.821	Osteitis deformans of right upper arm
M88.822	Osteitis deformans of left upper arm
M88.829	Osteitis deformans of unspecified upper arm
M88.831	Osteitis deformans of right forearm
M88.832	Osteitis deformans of left forearm
M88.839	Osteitis deformans of unspecified forearm
M88.841	Osteitis deformans of right hand
M88.842	Osteitis deformans of left hand

M88.849	Osteitis deformans of unspecified hand
M88.851	Osteitis deformans of right thigh
M88.852	Osteitis deformans of left thigh
M88.859	Osteitis deformans of unspecified thigh
M88.861	Osteitis deformans of right lower leg
M88.862	Osteitis deformans of left lower leg
M88.869	Osteitis deformans of unspecified lower leg
M88.871	Osteitis deformans of right ankle and foot
M88.872	Osteitis deformans of left ankle and foot
M88.879	Osteitis deformans of unspecified ankle and foot
M88.88	Osteitis deformans of other bones
M88.89	Osteitis deformans of multiple sites
M88.9	Osteitis deformans of unspecified bone
M89.9	Disorder of bone, unspecified
M94.9	Disorder of cartilage, unspecified
N92.4	Excessive bleeding in the premenopausal period
N95.0	Postmenopausal bleeding
N95.1	Menopausal and female climacteric states
N95.8	Other specified menopausal and perimenopausal disorders
N95.9	Unspecified menopausal and perimenopausal disorder
P78.84	Gestational alloimmune liver disease
S12.9XXA	Fracture of neck, unspecified, initial encounter
Z79.3	Long term (current) use of hormonal contraceptives
Z79.51	Long term (current) use of inhaled steroids
Z79.52	Long term (current) use of systemic steroids
Z79.84	Long term (current) use of oral hypoglycemic drugs
Z79.891	Long term (current) use of opiate analgesic
Z79.899	Other long term (current) drug therapy