Overview

Useful For
Diagnosing and monitoring oncogenic osteomalacia
Possible localization of occult neoplasms causing oncogenic osteomalacia
Diagnosing X-linked hypophosphatemia or autosomal dominant hypophosphatemic rickets
Diagnosing familial tumoral calcinosis with hyperphosphatemia
Predicting treatment response to calcitriol or vitamin D analogs in patients with renal failure

Method Name
ImmunometricEnzymeAssay

NY State Available
Yes

Specimen

Specimen Type
Plasma EDTA

Specimen Required

Patient Preparation: Fasting preferred; nonfasting acceptable

Collection Container/Tube:Lavender top (EDTA)

Submission Container/Tube: Plastic vial

Specimen Volume: 1.5 mL

Forms
If not ordering electronically, complete, print, and send an Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume
0.5 mL

Reject Due To

<table>
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<th>Status</th>
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<tbody>
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<tr>
<td>Gross lipemia</td>
<td>OK</td>
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<tr>
<td>Gross icterus</td>
<td>OK</td>
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Specimen Stability Information
Test Definition: FGF23
Fibroblast Growth Factor 23, P

<table>
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<th>Time</th>
<th>Special Container</th>
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**Clinical and Interpretive**

**Clinical Information**

Fibroblast growth factor 23 (FGF23) is a major regulator of phosphate homeostasis. It may act in concert with several other less well-characterized phosphate regulators.

FGF23 is secreted primarily by bone, followed by thymus, heart, brain and, in low levels, by several other tissues. It is coexpressed with the X-linked phosphate-regulating endopeptides (PHEX). High serum phosphate levels stimulate FGF23 expression and secretion through as yet poorly understood mechanisms. PHEX appears to modulate this process, possibly in part through cleavage of FGF23. Only intact FGF23 is considered bioactive. It interacts with a specific receptor on renal tubular cells, decreasing expression of type IIa sodium/phosphate cotransporters, resulting in decreased phosphate reabsorption. In addition, gene transcription of 1-a-hydroxylase is downregulated, reducing bioactive 1,25-dihydroxy vitamin D (1,25-2OH-VitD), thereby further decreasing phosphate reabsorption. Eventually, falling serum phosphate levels lead to diminished FGF23 secretion, closing the feedback loop.

Measurement of FGF23 can assist in diagnosis and management of disorders of phosphate and bone metabolism in patients with either normal or impaired renal function. When FGF23 levels are pathologically elevated in individuals with normal renal function, hypophosphatemia, with or without osteomalacia, ensues. This can occur with rare, usually benign, mixed connective tissue tumors that contain characteristic complex vascular structures, osteoclast-like giant cells, cartilaginous elements, and dystrophic calcifications. These neoplasms secrete FGF23 ectopically and autonomously (oncogenic osteomalacia). In less than one-fourth of cases a different benign or malignant, soft tissue tumor type, or, extremely rarely, a carcinoma, may be the cause of paraneoplastic FGF23 secretion. In either scenario, complete removal of the tumor cures the oncogenic osteomalacia.

Hypophosphatemia and skeletal abnormalities are also observed in X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR). In XLH, mutations of PHEX reduce its negative modulatory effect on bioactive FGF23 secretion. In ADHR, FGF23 mutations render it resistant to proteolytic cleavage, thereby increasing FGF23 levels. However, not all FGF23 mutations increase renal phosphate secretions. Mutations that impair FGF23 signaling, rather than increase its protease resistance, are associated with the syndrome of familial tumoral calcinosis (ectopic calcifications) with hyperphosphatemia.

In patients with renal failure, FGF23 contributes to renal osteodystrophy. The patient’s kidneys can no longer excrete sufficient amounts of phosphate. This leads to marked increases in FGF23 secretions in a futile compensatory response, aggravating the 1,25-2OH-VitD deficiency of renal failure and the consequent secondary hyperparathyroidism.

**Reference Values**

Results may be significantly elevated (ie, >900 RU/mL) in normal infants <3 months of age.

3 months-17 years: < or =230 RU/mL
> or =18 years: < or =180 RU/mL

**Interpretation**

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The majority of patients with oncogenic osteomalacia have fibroblast growth factor 23 (FGF23) levels above 2 times the upper limit of the reference interval. However, since the condition is a rare cause of osteomalacia, a full baseline biochemical osteomalacia workup should precede FGF23 testing. This should include measurements of the serum concentrations of calcium, magnesium, phosphate, alkaline phosphate, creatinine, parathyroid hormone (PTH), 25-hydroxy vitamin D (25-OH-VitD), 1,25-2OH-VitD, and 24-hour urine excretion of calcium and phosphate. Findings suggestive of oncogenic osteomalacia, which should trigger serum FGF23 measurements, are a combination of normal serum calcium, magnesium, and PTH; normal or near normal serum 25-OH-VitD; low or low-normal serum 1,25-2OH-VitD; low-to-profoundly low serum phosphate; and high urinary phosphate excretion.

Once oncogenic osteomalacia has been diagnosed, the causative tumor should be sought and removed. Complete removal can be documented by normalization of serum FGF23 levels. Depending on the magnitude of the initial elevation, this should occur within a few hours to a few days (half-life of FGF23 is approximately 20 to 40 minutes). Persistent elevations indicate incomplete removal of tumor. Serial FGF23 measurements during follow-up may be useful for early detection of tumor recurrence, or in partially cured patients, as an indicator of disease progression.

Because FGF23 has a short half-life, selective venous sampling with FGF23 measurements may be helpful in localizing occult tumors in patients with oncogenic osteomalacia. However, the most useful diagnostic cutoff for gradients between systemic and local levels has yet to be established.

X-linked hypophosphatemia (XLH) and most cases of autosomal dominant hypophosphatemic rickets (ADHR) present before the age of 5 as vitamin D-resistant rickets. FGF23 is significantly elevated in the majority of cases. Genetic testing provides the exact diagnosis. A minority of patients with ADHR may present later, as older children, teenagers, or young adults. These patients may have clinical features and biochemical findings, including FGF23 elevations, indistinguishable from oncogenic osteomalacia patients. Genetic testing may be necessary to establish a definitive diagnosis.

Patients with familial tumoral calcinosis and hyperphosphatemia have loss-of-function FGF23 mutations. The majority of these FGF23 mutant proteins are detected by FGF23 assays. The detected circulating levels are very high, in a futile compensatory response to the hyperphosphatemia.

Almost all patients with renal failure have elevated FGF23 levels, and FGF23 levels are inversely related to the likelihood of successful therapy with calcitriol or active vitamin D analogs. Definitive cutoffs remain to be established, but it appears that renal failure patients with FGF23 levels of more than 50 times the upper limit of the reference range have a low chance of a successful response to vitamin D analogues (<5% response rate).

Cautions
If being ordered as a tumor marker, do not interpret fibroblast growth factor 23 (FGF23) levels as absolute evidence for the presence or the absence of malignant disease. Results must be used in conjunction with information from the clinical evaluation of the patient and other diagnostic procedures.

Across the reference interval, FGF23 measurements in serum specimens are approximately 25 RU/mL lower than corresponding measurements obtained on EDTA plasma specimens. The validation and reference range study was performed using EDTA plasma. Serum should not be submitted for this test.

FGF23 levels must always be interpreted in conjunction with serum phosphate measurements, as FGF23 will be elevated in most other conditions that cause hyperphosphatemia in vivo. These include: renal failure, severe catabolic states (eg, severe systemic illness, uncontrolled type I diabetes mellitus, severe starvation), vitamin D toxicity, intravenous phosphate treatment and very high phosphate diets (eg, diets based largely on processed meats, processed cheese or other dairy products), advanced malignancy (particular with tumor lysis), crush or other significant muscle injury or destruction, fractures, and some endocrine disorders, in particular hypoparathyroidism and acromegaly. With the exception of renal failure, FGF23 measurements will not contribute to diagnosis or patient management in these situations.
Fasting specimens are preferred for FGF23 measurement. However, unless a substantial meal that is very phosphate-rich has been consumed (see above), nonfasting specimens are also acceptable. An average breakfast or small-to-medium sized meal will not elevate serum phosphate levels sufficiently to cause significant elevations in FGF23.

A minority of patients with oncogenic osteomalacia have FGF23 levels within the reference interval. It is thought that tumors in these individuals may be secreting different, as yet unidentified, phosphatoninins. Therefore, if the clinical picture and general osteomalacia laboratory workup suggest strongly that the patient has oncogenic osteomalacia; a normal FGF23 level should not always discourage tumor search or removal. Other putative phosphatoninins that may be secreted by tumors causing oncogenic osteomalacia include frizzled-related protein 4 and matrix extracellular protein.

Whenever the test results do not fit the clinical picture, the laboratory should be consulted regarding possible assay interference. As in every immunometric enzyme assay, severe lipemia, hemolysis, or hyperbilirubinemia may interfere in the assay. Although the assay contains blocking reagents, heterophile antibody interference may also rarely occur in certain patient specimens, usually resulting in false-positive results.

**Supportive Data**

During the validation of this assay we received 41 samples from 20 patients with suspected oncogenic osteomalacia for fibroblast growth factor 23 (FGF23) testing. The specimens originated from both outside and within Mayo Clinic. Fourteen patients had 15 FGF23 measurements within the normal reference range. Six patients had at least 1 elevated FGF23 measurement. Of these 6 patients, 3 patients underwent surgery for tumors that were thought to be causative. We were able to obtain preoperative (diagnostic) and postoperative blood specimens in these 3 patients. The FGF23 results were consistent with the outcomes:

<table>
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<th>Patient #</th>
<th>Preop</th>
<th>Postop</th>
<th>Further Follow-up</th>
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<tr>
<td>1</td>
<td>1,240</td>
<td>64</td>
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<td>Cured</td>
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<td>2</td>
<td>952</td>
<td>280</td>
<td>477, 282, 474, 566</td>
<td>Incomplete cure/recurrence</td>
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<tr>
<td>3</td>
<td>1,640</td>
<td>156</td>
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Of the other 3 patients with elevated FGF23 levels, 1 patient with clinical and biochemical findings that supported the diagnosis of oncogenic osteomalacia underwent selective venous sampling to localize the FGF23 source. All 14 samples taken during the procedure had markedly elevated FGF23 levels, with no significant gradient to peripheral venous level. Localization of the putative tumor failed. For the remaining 2 patients with elevated FGF23 levels we have no further clinical information.

**Clinical Reference**


**Performance**

**Method Description**

The kit uses 2 affinity purified goat antibodies that bind at the carboxy terminal portion of fibroblast growth factor 23 (FGF23). One antibody is coated onto microtiter wells and the other is biotinylated. Horseradish peroxide conjugated to avidin and 3,3', 5,5'-tetramethylbenzidine (TMB) substrate provide the colored product, which is read in a microtiter plate spectrophotometer.(Jonsson KB. Zahradnik R. Larsson T, et al: Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med 2003;348:1656-1663)

**PDF Report**

No

**Day(s) and Time(s) Test Performed**

Tuesday, Thursday; 10 a.m.

**Analytic Time**

1 day

**Maximum Laboratory Time**

8 days

**Specimen Retention Time**

3 months

**Performing Laboratory Location**

Rochester

**Fees and Codes**

**Fees**

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

**Test Classification**

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

**CPT Code Information**

83520

**LOINC® Information**
Test Definition: FGF23
Fibroblast Growth Factor 23, P

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