Corporate Medical Policy

Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing
AHS – G2164

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Description of Procedure or Service

Parathyroid hormone (PTH), along with calcitriol and fibroblast growth factor 23, regulate calcium and phosphate homeostasis. PTH modulates the serum ionized calcium concentration by stimulating kidney reabsorption of calcium as well as increasing bone resorption within minutes of PTH secretion. Primary hyperparathyroidism presents itself with hypercalcemia and elevated PTH levels and is typically caused by parathyroid adenoma or hyperplasia. Secondary hyperparathyroidism is seen “in patients with kidney failure who have…increased secretion of PTH [and] is related not only to gland hyperplasia and enlargement but also to reduced expression of CaSRs [calcium-sensitive receptors] and, perhaps, its downstream signaling elements (Fuleihan & Brown, 2017).”

Calcium is an essential metal found in its biologically relevant divalent cation (Ca$^{2+}$) form in vivo. It is involved in many important biological processes, including cell signaling, signal transduction, and muscle contraction. Only 45% of the plasma calcium is in the ionized form (or ‘free’ form), which is the physiologically active form, while the rest is bound to albumin or complexed to anions, such as phosphate or citrate (Hogan & Goldfarb, 2018). Both total calcium and ionized calcium can be tested from a blood sample. Occasionally, calcium concentration is determined from a 24-hour urine sample (AACC, 2014; Fuleihan & Silverberg, 2017).

Phosphorus, a nonmetal, is typically used in its oxidized phosphate polyatomic ionic form (PO$_4^{3-}$) in vivo and is an important functional group in all classes of biomolecules—carbohydrates, proteins, lipids, and nucleic acids. The cytosol uses a phosphate-based buffer to maintain pH homeostasis. Plasma phosphorus can be in either organic or inorganic form, but the inorganic phosphates are regulated by hormones, primarily PTH. Typically, phosphate/phosphorus testing is performed on a blood sample—even though only 1% of the total phosphate concentration can be found in the blood; however, phosphate testing can also be performed on a urine sample (AACC, 2013; Hogan & Goldfarb, 2018).

Magnesium, like calcium, in vivo is in its divalent cation (Mg$^{2+}$) form. It is involved in many enzymatic mechanisms as well as structural functions for both proteins and nucleic acids. Magnesium is required for maintenance of bone health as well as proper nerve conduction, muscle contraction, and energy production. Currently, magnesium is tested from a blood sample or less frequently from a 24-hour urine sample. Since only approximately 1% of the total magnesium concentration is available in the blood, “it is difficult to get an accurate measurement of total magnesium content from blood tests alone…[but] is still useful for evaluating a person’s magnesium status (AACC, 2017).”

Related Policy:
Vitamin D Testing

***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.
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Policy

BCBSNC will provide coverage for Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing when it is determined the medical criteria or reimbursement guidelines below are met.

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 Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing is covered

1. Reimbursement is allowed for serum intact parathyroid (PTH) testing in the following situations:
   a. To assess possible hyperparathyroidism; OR
   b. To assess post-operative results of parathyroid surgery; OR
   c. As part of annual testing of a patient previously diagnosed with hyperparathyroidism; OR
   d. As part of assessment of chronic kidney disease (CKD); OR
   e. As part of assessment of osteoporosis; OR
   f. As part of diagnosis and/or assessment of cancer or cancer therapy.

2. Reimbursement is allowed for Serum intact parathyroid (PTH) testing in cases of possible hypoparathyroidism, pseudohypoparathyroidism, or related disorders* (See Note 1 in the following situations:
   a. In initial assessment and diagnosis of the disorders listed in Note 1; OR
   b. To monitor disease and/or therapy.

NOTE 1: Conditions of hypoparathyroidism, pseudohypoparathyroidism, and related disorders (Mantovani et al., 2018)

1. Hypoparathyroidism
2. Pseudohypoparathyroidism Type 1A (PHP1A)—due to maternal loss of function mutation at the GNAS coding sequence
3. Pseudohypoparathyroidism Type 1B (PHP1B)—due to methylation defect at the GNAS coding sequence
4. Pseudopseudohypoparathyroidism (PPHP)—due to paternal loss of function mutation at the GNAS coding sequence
5. Progressive Osseous Heteroplasia (POH)—due to paternal loss of function mutation at the GNAS coding sequence
6. Acrodysostosis (ACRDYS1)—due to mutation in PRKAR1A
7. Acrodysostosis (ACRDYS2)—due to mutation in PDE4D

When Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing is not covered

3. Reimbursement is not allowed for Serum intact parathyroid (PTH) testing in screening of patients for asymptomatic hyperparathyroidism.

4. Reimbursement is not allowed for the following tests for individuals in general encounters without abnormal findings or wellness visits:
   a. Serum, blood, or fecal magnesium testing
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b. Serum phosphorus or phosphate testing
c. Urine phosphorus or phosphate testing
d. Serum total calcium, serum ionized calcium, or urine calcium testing
e. Serum parathyroid hormone testing

5. Reimbursement is not allowed for testing serum for truncated parathyroid hormone metabolites, including amino-terminal and carboxy-terminal fragments

Policy Guidelines

Background
Parathyroid hormone (also called parathormone or PTH) is a peptide hormone that is 84 amino acids long when first secreted by the parathyroid gland. It has a biological half-life of approximately 2-4 minutes before being proteolyzed into smaller fragments. These truncated fragments can comprise as much as 95% of the total circulating immunoreactive PTH. PTH is released whenever the serum ionized calcium concentration decreases as detected by the calcium-sensing receptor. Once released, PTH can increase serum calcium concentrations by increasing bone resorption as well as decreasing renal calcium excretion and increasing calcitriol production (Fuleihan & Brown, 2017). The bar graph figure below is taken from Valcour et al., 2018, and it shows the predominance of the truncated fragments circulating in hemodialysis patients. These truncated PTH peptides can interfere with many serum PTH testing methods (Fuleihan & Juppner, 2018; Valcour et al., 2018).

Both PTH and PTH-related protein analogues may assist in osteoporosis therapy as each play a key role in bone metabolism; it is widely accepted that PTH is an important regulator of calcium homeostasis in the body (Wojda & Donahue, 2018). PTH has been FDA approved as an anabolic treatment for osteoporosis (Wojda & Donahue, 2018). The PTH hormone analog teriparatide is known to stimulate bone remodeling, increase the mineral density in the hip and spine bones, and reduce the risk of fractures in postmenopausal osteoporotic women (Leder, 2017). Some patients with elevated PTH levels also exhibit vitamin D deficiency, while others do not; however, elevated PTH levels seem to affect both postural stability and muscle function (Bislev, Langagergaard Rodbro, Sikjaer, & Rejnmark, 2019). More research needs to be completed in this area.

Hyperthyroidism occurs when the thyroid is overactive and produces too much of the hormone thyroxine. Hyperthyroidism is caused by high serum phosphate levels, low serum calcium levels and...
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abnormal PTH levels; this disease is rare and can be managed with active vitamin D and calcium supplements (Marcucci, Della Pepa, & Brandi, 2017). Researchers have noted that treatment with recombinant human parathyroid hormone (rhPTH) may be a good treatment option for patients with hyperthyroidism who cannot maintain normal urinary and serum calcium levels (Marcucci et al., 2017).

The amount of calcium in the blood stream is monitored by the parathyroid glands. These glands release PTH, which increases blood calcium levels. Magnesium modulates parathyroid hormone secretion; particularly, high magnesium levels increase PTH when the parathyroid glands are exposed to low calcium levels (Rodriguez-Ortiz et al., 2014). Serum calcium may be high due to primary hyperthyroidism and malignancy, or low due to hypothyroidism or renal failure; abnormal serum calcium levels may lead to bone abnormalities or issues in the kidneys, the parathyroid gland, or the gastrointestinal tract (Shaker & Deftos, 2018).

Hypercalcemia is defined as high calcium levels in the blood stream; this may be caused by hyperparathyroidism, drugs, malignancy, or granulomatous disorders (Han, Fry, Sharma, & Han, 2019). Hypercalcemia caused by PTH is the most common cause of primary hyperthyroidism. “Algorithms for diagnosis of PTH related hypercalcaemia require assessment of a 24-h urinary calcium and creatinine excretion to calculate calcium/creatinine clearance ratio and radiological investigations including ultrasound scan and 99mTc-sestamibi-SPECT/CT (Han et al., 2019).”

Serum phosphate homeostasis is principally regulated by the work of PTH and fibroblast growth factor 23 (FGF23) via vitamin D. PTH primarily regulates calcium metabolism with secondary effects on phosphate whereas FGF23 is the opposite. Primary hyperparathyroidism (PHPT) often results in hypophosphataemia, but PTH resistance either due to surgical ablation or autoimmune disorders can cause hyperphosphatemia. PTH increases the release of phosphate from bone and the absorption of intestinal phosphate, but it increases the renal excretion of phosphate (Lederer, 2014). Typically, serum magnesium homeostasis is regulated by the kidneys. However, large increases in PTH increases bone resorption and can also affect the loop of Henle, the location of magnesium reabsorption in the kidneys, to decrease magnesium excretion (Quamme, 1986). Certain types of tumor cells, including esophageal squamous cell carcinomas (ESCC) release a parathyroid hormone-related protein (PTH-rP). A study by Konishi and colleagues has demonstrated that PTH and PTH-rP affect magnesium homeostasis in ESCC receiving cisplatin therapy. They found that “intravenous Mg supplementation therefore conferred protective effects against cisplatin-induced nephrotoxicity in patients with ESCC. Futhermore, increases in PTH or PTH-rP may have influenced the extent of nephrotoxicity (Konishi et al., 2018).”

Typically, serum magnesium homeostasis is regulated by the kidneys. However, large increases in PTH increases bone resorption and can also affect the loop of Henle, the location of magnesium reabsorption in the kidneys, to decrease magnesium excretion (Quamme, 1986). Certain types of tumor cells, including esophageal squamous cell carcinomas (ESCC) release a parathyroid hormone-related protein (PTH-rP). A study by Konishi et al. (2018) has demonstrated that PTH and PTH-rP affect magnesium homeostasis in ESCC receiving cisplatin therapy. The researchers found that “intravenous Mg supplementation therefore conferred protective effects against cisplatin-induced nephrotoxicity in patients with ESCC. Futhermore, increases in PTH or PTH-rP may have influenced the extent of nephrotoxicity (Konishi et al., 2018).” Hernandez-Becerra et al. (2020) recently found that, in rats, a calcium deficiency due to diet results in less magnesium identified in bones, including an apparent lower bone mineral density and a thinner cortical bone and trabecular bone porosity.

Analytical Validity
The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established a Working Group to research how pre-analytical conditions affected the measurement of PTH in blood samples (Hanon, Sturgeon, & Lamb, 2013). Their extensive review covered everything from circadian rhythms and how time of day affected clinical validity to storage conditions and seasonal changes. Their research included data from 83 different studies. They note that the inclusion of EDTA to the
sample will increase the stability to at least 72 hours for plasma samples and to 24 hours for serum samples. PTH concentrations in the summer are lower than in the winter months for patients in the Northern hemisphere, and that “PTH has a circadian rhythm characterized by a nocturnal acrophase and mid-morning nadir.” They note that the data are contradictory concerning the validity of results obtained from frozen samples regardless of whether the sample was stored at -20°C or -80°C. They found that PTH concentrations are considerably higher in central blood as compared to peripheral blood (median values of 24.3 pmol/L versus 15.3 pmol/L, respectively). They “recommend that blood samples for PTH measurement should be taken into tubes containing EDTA, ideally between 10:00 [a.m.] and 16:00 [p.m.], and plasma separated within 24 h of venipuncture. Plasma samples should be stored at 4°C and analysed within 72 h of venipuncture. Particular regard must be paid to the venipuncture site when interpreting PTH concentration. Further research is required to clarify the suitability of freezing samples prior to PTH measurement (Hanon et al., 2013).”

The IFCC Working Group on PTH also investigated how to improve PTH testing, especially with regards to the need for common references and standards. “Recent increases in understanding of the complex pathophysiology of CKD, which involves calcium, phosphate and magnesium balance, and is also influenced by vitamin D status and fibroblast growth factor (FGF)-23 production, should facilitate such improvement. Development of evidence-based recommendations about how best to use PTH is limited by considerable method-related variation in results, of up to 5-fold, as well as by lack of clarity about which PTH metabolites these methods recognize. This makes it difficult to compare PTH results from different studies and to develop common reference intervals and/or decision levels for treatment (Sturgeon et al., 2017).” The graph below (taken from (Almond, Ellis, & Walker, 2012; Sturgeon et al., 2017)) compares the differences between various available PTH assays observed within a single patient specimen.

The study by Almond and colleagues (Almond et al., 2012) shows that up to 4.2-fold differences can occur between these testing methods, and “these differences were sufficient to have treatment implications for 79% of the patients in the pilot study.” The 2017 IFCC study shows that “within-laboratory within-method coefficients of variation (CVs) <10%”; however, “between-laboratory between-method CVs are generally >20%” (Sturgeon et al., 2017).

Bensalah et al. (2018) analyzed the differences in PTH serum measurement between the Roche Cobas e411® (which uses a chemiluminescent sandwich enzyme immunoassay) and the Abbott Architect ci8200® (which uses a chemiluminescent microparticle immunoassay); this study included 252 patients. The two techniques were compared by the Bland-Altman difference diagram. “In conclusion, our study shows a great discrepancy between the results of the PTH assay on the Architect ci8200
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versus the Cobas e411™, suggesting that currently marketed kits need to be evaluated further (Bensalah et al., 2018).

Clinical Validity and Utility
Since serum PTH testing can be complicated by the presence of proteolytic fragments as well as a brief biological half-life of mere minutes, Valcour and associates evaluated the efficacy of the LIAISON 1-84 PTH test, a third-generation serum test, as compared to other intact testing methods. Their study was conducted at three different locations throughout the United States. Each test site recruited fifteen patients, and the patients were equally divided into three groups—healthy patients, primary hyperparathyroid patients, and hemodialysis patients. A minimum of nine samples were collected from each patient. They also evaluated each test’s efficacy concerning how the sample was collected (plasma EDTA, unspun plasma EDTA, and serum separator) as well as how storage time at room temperature affected results (up to 72 hours). They used two different standards—the WHO 95/646 international standard and the synthetic Bachem PTH(1-84) standard. Both the second- and third-generation intact PTH test were consistent with the standards up to 72 hours; however, the “serum is significantly less stable than plasma when samples are stored at room temperature for 72 h regardless of platform, even when separated from the clot by centrifugation within 1 h.” The mean percent change from baseline ranged from 96%-107% for the LIAISON 1-84 test except for the serum at 72 h, which had a mean of 82%. Likewise, the second-generation mean percent change from baseline ranged from 95%-108% except for the serum at 72 h, which again was 82%. The authors conclude that the “LIAISON 1-84 PTH assay is accurate and reliably measures the biologically active PTH molecule in plasma or serum stored at room temperature for up to 27 and 24 h, respectively (Valcour et al., 2018).”

A study at the Cleveland Clinic of more than 2.7 million patients’ electronic medical records was published in 2013 looking at the prevalence of PHPT, both symptomatic and asymptomatic, and the correlation with serum calcium testing. Of the records obtained, 2% had serum calcium levels >10.5 mg/dL, and 1.3% of the total patient population had previously been diagnosed with PHPT. Only 32% of the patients who had not been previously diagnosed with either hypercalcemia, PHPT, or had undergone a parathyroidectomy had recorded PTH values in their medical records. “Patients with calcium of 11.1 – 11.5 mg/dL were most likely to have PHPT (55%). Patients with calcium >12 mg/dL were most likely to have PTH measured. Of hypercalcemic patients, 67% never had PTH obtained, …. It is estimated that 43% of hypercalcemic patients are likely to have PHPT….” They conclude, “it is crucial to evaluate even mild hypercalcemia, because 43% of these patients have PHPT. PHPT is underdiagnosed and undertreated (Press et al., 2013).”

In 1975, Pak and colleagues published their results of a urine test they developed to diagnose hypercalciuria (Pak, Kaplan, Bone, Townsend, & Waters, 1975). Since then, 24-hour urinary calcium testing is a common clinical practice, especially in monitoring kidney health, with reference values of <250 mg/24 hours for males and <200 mg/24 hours for females (Mayo, 2018a). A comprehensive study by Curhan and colleagues (Curhan, Willett, Speizer, & Stampfer, 2001) investigated the 24-hour urine concentrations of calcium, magnesium, and phosphorus along with several other analytes. Calcium and magnesium were quantified by atomic absorption spectroscopy whereas phosphorus was measured using a Cobas centrifugal analyzer. They collected samples from over 1000 patients who were already taking part in three large-scale ongoing cohort studies—NHS I, NHS II, and HPFS. Neither magnesium nor phosphate was significant in any of the three cohorts between the patients with kidney stones and the controls; however, the urine calcium concentration was significantly elevated (p ≤ 0.01) in two of the three cohorts. One cohort, though, had 27% of the patients in the control group exhibiting hypercalciuria and only 33% of the experimental group exhibiting hypercalciuria. They conclude that “the traditional definitions of normal 24-hour urine values need to be reassessed, as a substantial proportion of controls would be defined as abnormal… (Curhan et al., 2001).”

Serum magnesium testing can be used in monitoring preeclampsia and hypermagnesemia. The reference values are age-dependent, but levels greater than 9.0 mg/dL can be life-threatening (Mayo,
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2018b). The evidence of causation or the use of serum magnesium in predicting preeclampsia have been inconclusive. A study by Kreekala and associates (Kreekala, Kitpornthenanun, Sangwipasnaporn, Rungsrithananon, & Wattanavaekin, 2018) has proposed the use of serum total magnesium and ionized magnesium levels to develop a magnesium-based equation for screening of preeclampsia. Their study involved 84 pregnant women with 20 of them being controls. The remaining 64 had been diagnosed with preeclampsia after the 20th week of pregnancy. They determined that the serum ionized magnesium levels were “significantly lower in preeclampsia group (23.95 ± 4.7% vs. 26.28 ± 2.3%, p = .04).” The equation they developed has an “area of ROC for predictive accuracy of the model [of] 0.77 (p < .001)… [The] ROC suggested that the score of 0.27 would be a threshold for screening preeclampsia with 70% sensitivity and 81% specificity.” They suggest “blood testing on total and ionized magnesium concentrations as well as calculation of ionized magnesium fraction in addition to routine antenatal care for better screening of the disease (Kreekala et al., 2018).”

Applicable State and Federal Regulations

The FDA has approved many different tests and assays for parathyroid hormone. A search of the FDA Device Database on 1/14/2020 yielded twenty results for parathyroid hormone in general whereas nine specific tests have been approved for “intact parathyroid hormone.” Likewise, a search of calcium test yielded twenty-four results for FDA-approved tests. A search using the term “phosphorus test” has fifteen results while “phosphorous test,” another term used at times in clinical labs, had two pertinent results. A search using “phosphate test” returned nine results for this policy as of 1/14/2020. An FDA database search using “magnesium test” as search criteria yielded fourteen different FDA-approved tests (FDA, 2018).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (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 this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

2016 American Association of Endocrine Surgeons (AAES) (Wilhelm, Wang, Ruan, & et al., 2016)

The AAES released their guidelines concerning primary hyperparathyroidism (pHPT) in 2016. With respect to laboratory testing, in Recommendation 1-1, they state, “The biochemical evaluation of suspected pHPT should include serum total calcium, PTH, creatinine, and 25-hydroxyvitamin D levels (strong recommendation; moderate-quality evidence).” They do address differentiating between pHPT and suspected “familial hypocalciuric hypercalcemia, which is an autosomal dominant disorder of the renal calcium-sensing receptor that can mimic pHPT.” In Recommendation 1-2 (strong recommendation; moderate-quality evidence), “a 24-hour urine measurement of calcium and creatinine should be considered in patients undergoing evaluation for possible pHPT…. Familial hypocalciuric hypercalcemia should be considered in patients with long-standing hypercalcemia, urinary calcium levels less than 10 mg/24 hours, and a calcium to creatinine clearance ratio less than 0.01.” They also address the use of intraoperative PTH monitoring (IPM). Recommendation 6-1: “When image-guided focused parathyroidectomy is planned, IPM is suggested to avoid higher operative failure rates (strong recommendation; moderate-quality evidence).” However, they give a strong recommendation with low-quality evidence to recommendation 6-2: “Surgeons who use IPM should use a sampling protocol that is reliable in the local environment and should be familiar with the interpretation of PTH decay dynamics.” They do not state the frequency of testing either calcium or PTH post-operatively, but they state in multiple recommendations comments concerning monitoring or measuring calcium and/or PTH levels or determining post-operative hyper-/hypoparathyroidism (Recommendation 14-7, Recommendation 15-1a, Recommendation 15-1b, Recommendation 15-3, Recommendation 15-4, and Recommendation 16-2). They also state that the
definition of a success versus failure of operation is when levels are compared six months post-operation.

2018 First International Consensus Statement on Pseudohypparathyroidism and Related Disorders (Mantovani et al., 2018)

An international consortium of representatives from across Europe and North America released their first international consensus statement, including extensive guidelines and recommendations, concerning pseudohypparathyroidism and related disorders in 2018. These disorders have a wide array of phenotypes but are due to impaired cell signaling cascades of G-protein coupled receptors (GPCRs). Pseudohypparathyroidism can be classified as either type 1A or 1B (PHP1A and PHP1B, respectively), depending on the type of defect in the GNAS coding sequence. Pseudopseudohypparathyroidism (PPHP) and progressive osseous heteroplasia (POH) are caused by a paternal loss of function defect to GNAS. Acrodysostosis is classified as either type 1 (ACRDYS1) or type 2 (ACRDYS2) due to mutations in either PRKAR1A or PDE4D, respectively. PTH resistance can be negligible in infancy but typically increases with age.

In recommendation 1.3 (A+++), they list the clinical and biochemical major criteria for diagnosing PHP and related disorders, including “PTH resistance, and/or subcutaneous ossifications that can include deeper ossifications, and/or early-onset (before 2 years of age) obesity associated with TSH resistance or with one of the above, and/or AHO [Albright hereditary osteodystrophy] alone” regardless of family history. In recommendation 1.6 (A+++), “The definition of PTH resistance is as follows: [1] The association of hypocalcaemia, hyperphosphataemia and elevated serum levels of PTH in the absence of vitamin D deficiency and when magnesium levels and renal function are normal. [2] PTH resistance in the context of PHP and related disorders should be suspected when PTH is at, or above, the upper limit of normal, in the presence of normal calcifediol levels and elevated serum levels of phosphorus, even in the absence of overt hypocalcaemia. PTH resistance and consequent changes in serum levels of calcium, phosphorus and PTH can be variable, and repeated testing might be required.” In all cases, genetic counseling is recommended.

In recommendation 3.2, they state that serum PTH, calcium, phosphorus, and calcifediol should be measured; moreover, “measurement of PTH, calcium and phosphorus should be performed regularly (every 6 months in children and at least yearly in adults) with the exception of patients carrying either a GNAS mutation on the paternal allele or a PDE4D mutation in whom, apart from diagnosis, routine assessment is not necessary. Monitoring of serum levels of calcium should be more frequent in symptomatic individuals, during acute phases of growth, during acute illness and during pregnancy and breastfeeding…..” For patients undergoing vitamin D therapy, they stress as part of recommendation 3.4 (A++) that serum phosphate be monitored. Concerning patients undergoing treatment for PTH resistance, in recommendation 3.5 (A++), they state that “levels of PTH, calcium and phosphorus should be monitored every 6 months in asymptomatic patients and more frequently when clinically indicated.” In recommendation 3.26 (A+), they do not recommend routinely measuring calcitonin.

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

The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism convened in 2014 and published their guidelines as a consensus statement in The Journal of Clinical Endocrinology & Metabolism. As for monitoring patients with asymptomatic primary hyperparathyroidism (PHPT), they recommend annual testing of serum calcium. They give the formula to determine corrected calcium concentration, which they recommend using rather than free calcium, since “most centers do not have sufficient capabilities to rely upon an ionized, free calcium concentration”:

Corrected [Ca] = [total serum calcium in mg/dL + 0.8*(4.0 - patient’s serum albumin in g/dL)]
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They list their recommendations for evaluating asymptomatic PHPT in Table 3 shown below although they do state that “this evaluation is for PHPT, not to distinguish between PHPT and other causes of hypercalcemia.” This table includes calcium (both serum and 24-hour urine testing) and phosphate testing.

<table>
<thead>
<tr>
<th>Table 3. Recommendations for the Evaluation of Patients With Asymptomatic PHPT</th>
</tr>
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<tbody>
<tr>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td>Biochemistry panel (calcium, phosphate, alkaline phosphate, activity, BUN, creatinine), 25(OH)D</td>
</tr>
<tr>
<td>PTH by second- or third-generation immunoassay</td>
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<tr>
<td>BMD by DXA</td>
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<tr>
<td>Lumbar spine, hip, and distal 1/3 radius</td>
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<tr>
<td>Vertebral spine assessment</td>
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<tr>
<td>X-ray or VFA by DXA</td>
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<tr>
<td>24-h urine for:</td>
</tr>
<tr>
<td>Calcium, creatinine, creatinine clearance</td>
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<tr>
<td>Stone risk profile</td>
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<tr>
<td>Abdominal imaging by x-ray, ultrasound, or CT scan</td>
</tr>
<tr>
<td>Optional</td>
</tr>
<tr>
<td>HRpQCT</td>
</tr>
<tr>
<td>TBS by DXA</td>
</tr>
<tr>
<td>Bone turnover markers (bone-specific alkaline phosphatase activity, osteocalcin, PINP [select one], serum CTX, urinary NTX [select one])</td>
</tr>
<tr>
<td>Fractional excretion of calcium on timed urine sample</td>
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<tr>
<td>DNA testing if genetic basis for PHPT is suspected</td>
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</tbody>
</table>

In their algorithm for monitoring patients with normocalcemic PHPT they include annual calcium and PTH testing; however, there is no mention of the method of calcium testing (i.e. serum versus 24-hour urine testing) or phosphate testing.

2018 National Comprehensive Cancer Network (NCCN)
The NCCN addresses PTH, calcium, phosphate, and magnesium testing in several different guidelines.

*Neuroendocrine & Adrenal Tumors (NCCN, 2018i):* In the section concerning Multiple Endocrine Neoplasia, Type 1 (MEN1), the NCCN added PTH and serum calcium in the diagnosis and clinical evaluation of suspected MEN1. They also state that both calcium and PTH are to be checked annually as part of MEN1 surveillance protocol. “The panel recommends annual calcium levels to screen for parathyroid tumors. If calcium levels rise, serum PTH and 25-OH vitamin D should be measured and imaging with neck ultrasound and/or parathyroid sestamibi should be performed.” Likewise, for Multiple Endocrine Neoplasia, Type 2 (MEN2), both serum calcium and PTH are recommended for diagnosis and evaluation. They also recommend evaluation of calcium and PTH post-operatively following a parathyroidectomy.

*Acute Lymphoblastic Leukemia (ALL) (NCCN, 2018a):* As part of the initial workup for ALL patients, they recommend “a tumor lysis syndrome panel (including measurements for serum lactate dehydrogenase [LDH], uric acid, potassium, phosphates, and calcium).” In the section concerning the supportive care of ALL in steroid management, they state to “obtain vitamin D and calcium status and replete as needed” to monitor possible osteonecrosis associated as a potential long-term side effect of corticosteroids.
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*Systemic Light Chain Amyloidosis (NCCN, 2018l)*: As part of the initial diagnostic workup, in the section titled “Laboratory evaluation (directed toward commonly affected organ systems),” they recommend testing “serum BUN/creatinine, electrolytes, albumin, and calcium.”

*Bladder Cancer (NCCN, 2018b)*: In the table showing follow-up testing and treatments post-cystectomy, they recommend “bone testing” that consists of checking the blood levels of calcium, magnesium, phosphate, and alkaline phosphatase.

*Bone Cancer (NCCN, 2018c)*: In the section concerning the workup of Giant Cell Tumor of Bone (GCTB), a rare benign tumor, they state that “brown tumor of hyperparathyroidism should be considered as a differential diagnosis, though routine evolution of serum calcium, phosphate, and parathyroid hormone levels can help exclude this diagnosis.”

*Breast Cancer (NCCN, 2018d)*: Since metastatic breast cancer can be treated with bisphosphonate, they recommend “an initial evaluation of serum calcium, creatinine, phosphorous, and magnesium levels [to] be undertaken prior to the initiation of intravenous bisphosphonate treatment or subcutaneous denosumab treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous, and magnesium may be prudent since hypophosphatemia and hypocalcemia have been reported.” In general, in monitoring metastatic disease, “laboratory tests such as alkaline phosphatase, liver function, blood counts, and calcium” are to be included to help aid the clinician in determining “the effectiveness of treatment and the acceptability of toxicity.”

*Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) (NCCN, 2018e)*: Small-molecule inhibitors, such as Venetoclax, are possible therapies for CLL/SLL. Tumor Lysis Syndrome (TLS) is a possible side effect of such treatment. In the section on supportive care for CLL/SLL, they recommend “TLS prophylaxis for patients at high risk for TLS, including those with bulky disease and those with progressive disease after small-molecule inhibitor therapy.” To monitor possible TLS, potassium, uric acid, phosphorous, calcium, and lactate dehydrogenase are recommended for testing. In Venetoclax therapy, particularly, they state to “evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.” The table below (adapted from (NCCN, 2018e)) depicts the blood chemistry monitoring as recommended:

<table>
<thead>
<tr>
<th>Blood Chemistry Monitoring (potassium uric acid, phosphorus, calcium and creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Tumor Burden</strong></td>
</tr>
<tr>
<td>Outpatient setting</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Medium Tumor Burden</strong></td>
</tr>
<tr>
<td>Outpatient setting</td>
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<tr>
<td><strong>High Tumor Burden</strong></td>
</tr>
<tr>
<td>In hospital setting</td>
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</tbody>
</table>
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<table>
<thead>
<tr>
<th>Outpatient setting (for subsequent ramp-up doses)</th>
<th>Pre-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6-8 hrs</td>
</tr>
<tr>
<td></td>
<td>24 hrs</td>
</tr>
</tbody>
</table>

Esophageal and Esophagogastric Junction Cancers (NCCN, 2018f): In the section on principles of survivorship under Management of Long-Term Sequelae of Disease or Treatment, they say to “consider monitoring vitamin B, folic acid, vitamin D, and calcium levels.” Moreover, following esophagectomy, long-term calcium deficiency is common along with deficiencies in vitamin B₁₂, folic acid, and vitamin D.

Kidney Cancer (NCCN, 2018g): The NCCN uses serum calcium levels as a predictor “of short survival used to select patients for Temsirolimus” as well as a prognostic factor [i.e. “calcium > upper limit of normal (Normal: 8.5-10.2 mg/dL)’’]. They do not state how frequently serum calcium should be tested or if it is solely for use at diagnosis.

Multiple Myeloma (NCCN, 2018h): In the initial diagnostic workup for multiple myeloma, the NCCN recommends testing “serum BUN/creatinine, electrolytes, albumin, and calcium”. As follow-up to the clinical presentation of either “solitary osseous”, “active (symptomatic)”, or “smoldering (asymptomatic)” myeloma, again “corrected calcium” is listed as one of the recommended blood tests. Calcium is also recommended following treatment of active myeloma, and an elevated calcium concentration is listed as one of the “direct indicators of increasing disease and/or end organ dysfunction” since “excess bone resorption from myeloma bone disease can lead to excessive release of calcium.”

Occult Primary (Cancer of Unknown Primary [CUP]) (NCCN, 2018j): “Initial evaluation of a patient with a suspected metastatic malignancy should include a complete history and physical examination…. Routine laboratory studies (ie, CBC, electrolytes, liver function tests, creatinine, calcium), occult blood stool testing, and contrast-enhanced chest/abdominal/pelvic CT scans are also recommended.”

Prostate Cancer (NCCN, 2018k): In the section concerning the treatment with denosumab, they state that “hypocalcemia is seen twice as often with denosumab than zoledronic acid and all patients on denosumab should be treated with vitamin D and calcium with periodic monitoring of serum calcium levels”. In the section concerning patients with castration resistant prostate cancer (CRPC), they state, “hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required for denosumab and recommended for zoledronic acid, with repletion as needed.” In treatment of CRPC with abiraterone acetate, “monitoring of liver function, potassium and phosphate levels, and blood pressure readings on a monthly basis, at least initially is warranted during abiraterone/prednisone therapy.” Men with CRPC are at a higher risk for severe hypocalcemia and hypophosphatemia.

T-Cell Lymphomas (NCCN, 2018m): For adult T-Cell Leukemia/Lymphoma (ATLL), the NCCN states, “the initial workup for ATLL should include a complete history and physical examination…a CBC with differential and complete metabolic panel (serum electrolyte levels, calcium, creatinine, and blood urea nitrogen) and measurement of serum LDH levels.” Under the supportive care section for T-Cell lymphomas, they do recommend monitoring for TLS, which include measuring serum phosphorous and calcium levels since “laboratory TLS is defined as a 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels”.

Thyroid Carcinoma (NCCN, 2018n): In the algorithm for thyroid carcinoma-medullary carcinoma, both serum calcium and PTH are recommended as additional workup for patients who have MEN2A/Familial medullary thyroid carcinoma (codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations). Serum calcium testing is among the testing and procedures recommended upon diagnosis of medullary thyroid carcinoma.
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KDIGO released their Clinical practice guideline for the Evaluation and Management of Chronic Kidney Disease (CKD) in 2012 and then their Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) in 2017. In the 2012 guidelines (KDIGO, 2013), in recommendation 3.3.1 (1C), they state, “We recommend measuring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity at least once in adults with GFR <45 ml/min/1.73 m² (GFR categories G3b-G5) in order to determine baseline values and inform prediction equations if used.” In recommendation 3.3.4 (2C recommendation strength), for people in GFR categories G3b-G5 they “suggest that people with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency.” With regards to serum phosphate levels, they recommend that they are maintained “in the normal range according to local laboratory reference values” (recommendation 3.3.3; 2C). The guidelines, however, do not state a recommendation with respect to the frequency of testing past initial baseline and do not address magnesium testing other than to list renal magnesium wasting as a criterion for CKD.

The 2017 guidelines (KDIGO, 2017) in recommendation 3.1.1 state: “We recommend monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G3a (1C). In children, we suggest such monitoring beginning in CKD G2 (2D).” Recommendation 3.1.2 (Not graded) addresses the frequency of such testing and says “to base the frequency…on the presence and magnitude of abnormalities, and the rate of progression of CKD.” The table below lists the “reasonable monitoring intervals”:

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Test</th>
<th>Reasonable Monitoring Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3a-G3b</td>
<td>Serum Calcium</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>G3a-G3b</td>
<td>Serum Phosphate</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>G3a-G3b</td>
<td>PTH</td>
<td>“Based on baseline level and CKD progression”</td>
</tr>
<tr>
<td>G4</td>
<td>Serum Calcium</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>G4</td>
<td>Serum Phosphate</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>G4</td>
<td>PTH</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>G5</td>
<td>Serum Calcium</td>
<td>Every 1-3 months</td>
</tr>
<tr>
<td>G5</td>
<td>Serum Phosphate</td>
<td>Every 1-3 months</td>
</tr>
<tr>
<td>G5</td>
<td>PTH</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>G4-G5D</td>
<td>Alkaline Phosphatase</td>
<td>Every 12 months, or more frequently in the presence of elevated PTH</td>
</tr>
</tbody>
</table>

Recommendation 3.2.3 (2B) suggests measuring either PTH or bone-specific alkaline phosphatase to assess bone disease. For patients with CKD G3a-G5D, their treatment “should be based on serial assessments of phosphate, calcium, and PTH levels, considered together” (Recommendation 4.1.1 Not Graded). Recommendation 4.2.1 (2C) states: “In patients with CKD G3a-G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency.” Recommendation 5.2 (Not Graded) addressed the frequency of testing post-kidney transplant. The table below contains the information regarding the reasonable monitoring intervals:
## Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing

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<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Test</th>
<th>Reasonable Monitoring Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1T-G3bT</td>
<td>Serum Calcium</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>G1T-G3bT</td>
<td>Serum Phosphate</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>G1T-G3bT</td>
<td>PTH</td>
<td>Once, with subsequent intervals depending on baseline level and CKD progression</td>
</tr>
<tr>
<td>G4T</td>
<td>Serum Calcium</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>G4T</td>
<td>Serum Phosphate</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>G4T</td>
<td>PTH</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>G5T</td>
<td>Serum Calcium</td>
<td>Every 1-3 months</td>
</tr>
<tr>
<td>G5T</td>
<td>Serum Phosphate</td>
<td>Every 1-3 months</td>
</tr>
<tr>
<td>G5T</td>
<td>PTH</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>G3aT-G5T</td>
<td>Alkaline Phosphatase Activity</td>
<td>Annually, or more frequently in the presence of elevated PTH</td>
</tr>
</tbody>
</table>

Within recommendation 5.6 (2C), KDIGO recommends “treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (KDIGO, 2017).”

### 2013, 2014 American Urological Association (AUA) (Donat et al., 2013; Pearle et al., 2014)

In 2013, the AUA published *Follow-up for Clinically Localized Renal Neoplasms*. In recommendation 2, as an *Expert Opinion*, they state, “Patients undergoing follow-up for treated or observed renal masses should undergo basic laboratory testing to include blood urea nitrogen (BUN)/creatinine, urine analysis (UA) and estimated glomerular filtration rate (eGFR). Other laboratory evaluations, including complete blood count (CBC), lactate dehydrogenase (LDH), liver function tests (LFTs), alkaline phosphatase (ALP) and calcium level, may be used at the discretion of the clinician.”

The AUA published their guidelines titled *Medical Management of Kidney Stones* in 2014. In recommendation 2, they recommend that “clinicians should obtain serum intact parathyroid hormone (PTH) level as part of the screening evaluation if primary hyperparathyroidism is suspected.” They also recommend that “metabolic testing should consist of one or two 24-hour urine collections obtained on a random diet and analyzed at minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine” but that “clinicians should not routinely perform ‘fast and calcium load’ testing to distinguish among types of hypercalciuria” (Recommendations 6 & 7).

### 2013-2015 National Institute for Health and Care Excellence (NICE)

NICE, like the NCCN, addresses PTH, calcium, phosphate, and magnesium testing in several different guidelines.

### 2013 Chronic kidney disease (stage 4 or 5): management of hyperphosphataemia (NICE, 2013)

In recommendation 1.1.10 within the section concerning the use of phosphate binders, they state to “consider either combining with, or switching to, a non-calcium-based binder if hypercalcaemia develops (having taken into account other causes of raised calcium), or if serum parathyroid hormone levels are low.” Then, in recommendation 1.1.12: “For adults with stage 5 CKD who are on dialysis and who are taking a calcium-based binder, if serum phosphate is controlled by the current diet and phosphate binder regimen but: serum calcium goes above the upper limit of normal, or serum parathyroid hormone levels are low, consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having
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taken into account other causes of raised calcium.” These guidelines mention serum phosphate, serum
calcium, and PTH; however, they do not state when these tests should be performed or the frequency of
testing.

1.7.1, they do not recommend to “routinely measure calcium, phosphate, parathyroid hormone (PTH) and
vitamin D levels in people with a GFR of 30 ml/min/1.73 m² or more (GFR category G1, G2, or G3).”
Then, in the following recommendation, they do recommend measuring serum calcium, PTH, and
phosphate for patients in GFR categories G4 or G5. “Determine the subsequent frequency of testing by
the measured values and the clinical circumstances. Where doubt exists, seek specialist opinion.” They
recommend in 1.7.7 to “monitor serum calcium and phosphate concentrations in people receiving
alfacalcidol or calcitriol supplements.”

2014 Bipolar disorder: assessment and management (NCCMH, 2014): In recommendation 1.2.12, they
recommend annual calcium screening for anyone on a long-term lithium therapy regimen; however, in
recommendation 1.10.21, they recommend testing “for urea and electrolytes including calcium…every
six months, and more often if there is evidence of impaired renal or thyroid function, raised calcium levels
or an increase in mood symptoms that might be related to impaired thyroid function.” In recommendation
1.10.14, when a patient begins a lithium regimen, a clinician should test “for urea and electrolytes
including calcium, estimated glomerular filtration rate (eGFR), thyroid function and a full blood count”.

2014 Multiple sclerosis in adults: management (NICE, 2014b): In recommendation 1.1.4, they
recommend calcium testing along with full blood count, inflammatory markers, liver and renal function
tests, glucose, thyroid function tests, vitamin B₁₂, and HIV serology testing “before referring a person
suspected of having MS to a neurologist” to “exclude alternative diagnoses”.

2015 Suspected cancer: recognition and referral (NICE, 2015): In the section concerning myeloma, in
recommendation 1.10.4, they state, “offer a full blood count, blood tests for calcium and plasma viscosity
or erythrocyte sedimentation rate to assess for myeloma in people aged 60 and over with persistent bone
pain, particularly back pain, or unexplained fracture.”

2017 American Society of Clinical Oncology (ASCO)/Cancer Care Ontario (CCO) (Dhesy-Thind et al., 2017)
The CCO and ASCO convened a working group in 2017 concerning the use of bisphosphonates in breast
cancer and published their recommendations in the Journal of Clinical Oncology. They clearly state that
“patients should have serum calcium measured prior to starting treatment. Patients receiving intravenous
bisphosphonates (zoledronic acid) should be monitored for renal function prior to starting this treatment,
and for serum calcium and increase in serum creatinine throughout the treatment period.”

2016 American Association of Clinical Endocrinologists (AACE)/American College of
Endocrinology (ACE) (Camacho et al., 2016)
The AACE/ACE guidelines concerning osteoporosis in post-menopausal women recommends PTH,
phosphate, and 24-hour urine calcium testing in evaluating osteoporosis. They note that “the 24-hour
urine calcium collection must occur after the patient is vitamin D replete and has been on a reasonable
calcium intake (1,000-1,200 mg/day) for at least 2 weeks.”

2014 Society of Obstetricians and Gynaecologists of Canada (SOGC)(Magee, Pels, Helewa, Rey, &
von Dadelszen, 2014)
The 2014 SOGC guidelines concerning hypertensive disorders during pregnancy does recommend using
magnesium supplements for pregnant women; however, they clearly state in recommendation #120 that
“routine monitoring of serum magnesium levels is not recommended”.
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2013 Institute for Clinical Systems Improvement (ICSI) (NGC, 2013)

In the ICSI’s guidelines concerning adult heart failure, they recommend both magnesium and calcium testing for patients undergoing loop thiazide diuretics with frequency of “before diuretic initiation, then every four months for the duration of therapy”.

2016 American Academy of Pediatrics (AAP) (Tieder et al., 2016)

The AAP in 2016 issued guidelines concerning Brief Resolved Unexplained Events (BRUE) in infants. “The term BRUE is defined as an event occurring in an infant younger than 1 year when the observer reports a sudden, brief, and now resolved episode of ≥1 of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hyper- or hypotonia); and (4) altered level of responsiveness.” For infants between 60 days and <1 year in age, in recommendation 6B under IEM (inborn error of metabolism), they state that “clinicians should not obtain a measurement of serum sodium, potassium, chloride, blood urea nitrogen, creatinine, calcium, or ammonia to detect an IEM on infants presenting with a lower-risk BRUE (Grade C, Moderate Recommendation).”

2013 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)/The Obesity Society (TOS) (Gonzalez-Campoy et al., 2013)

The joint task force between AACE, ACE, and TOS issued Clinical Practice Guidelines for Healthy Eating for the Prevention and Treatment of Metabolic and Endocrine Diseases in Adults in 2013. With regards to CKD in recommendation R29, they state, “If the intact parathyroid hormone (PTH) level remains elevated above treatment goal despite a serum 25(OH)D level higher than 30 ng/mL, treatment with an active form of vitamin D is indicated (Grade A, BEL 1).” As part of recommendation R32, they state, “A 24-hour urine calcium collection should be measured in patients with osteoporosis or patients at risk for bone loss in order to check calcium adequacy and test for hypercalciuria or malabsorption (Grade B, BEL 2).” Furthermore, “during vitamin D therapy, serum calcium and phosphorus levels need to be monitored closely to prevent hypercalcemia and hyperphosphatemia, aiming for calcium and phosphorus levels of <10.2 mg/dL and <4.6 mg/dL, respectively.”

2013 AACE/TOS/ASMBS (American Society for Metabolic & Bariatric Surgery) (Mechanick et al., 2013)

Also, in 2013, the AACE/TOS/ASMBS issued guidelines concerning perioperative, nonsurgical support for the bariatric surgery patient. Within recommendation R48, they state, “Bisphosphonates may be considered in bariatric surgery patients with osteoporosis only after appropriate therapy for calcium and vitamin D insufficiency…. Evaluation should include serum parathyroid hormone (PTH), total calcium, phosphorus, 25-hydroxyvitamin D, and 24-hour urine calcium levels (Grade C; BEL 3).”

2013 American Gastroenterological Association (AGA) (Bharucha, Dorn, Lembo, & Pressman, 2013)

The 2013 AGA guidelines concerning constipation states that “although metabolic tests (thyroid-stimulating hormone, serum glucose, creatinine, and calcium) are often performed, their diagnostic utility and cost-effectiveness have not been rigorously evaluated and are probably low.” Under the section What Tests Should Be Performed to Assess for Medical Causes of Constipation?, they state, “In the absence of other symptoms and signs, only a complete blood cell count is necessary (strong recommendation, low-quality evidence). Unless other clinical features warrant otherwise, metabolic tests (glucose, calcium, sensitive thyroid-stimulating hormone) are not recommended for chronic constipation (strong recommendation, moderate-quality evidence).”

2015 National Blood Authority (NBA, 2015)

The National Blood Authority of Australia in their guidelines concerning obstetrics and maternity recommend testing ionized calcium levels in women with major obstetric hemorrhage. It is listed
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alongside several other criteria, such as hemoglobin and platelet count, and it “should be measured early and frequently”. Values of ionized calcium less than 1.1 mmol/L are “indicative of critical physiologic derangement”.

<table>
<thead>
<tr>
<th>Year &amp; Society</th>
<th>Condition</th>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016 AAES</td>
<td>PHPT</td>
<td>Serum Ca, PTH</td>
<td>Testing in evaluation of suspected PHPT; test at least one, if not both, six months post-parathyroidectomy</td>
</tr>
<tr>
<td>2016 AAES</td>
<td>PHPT/HCHC</td>
<td>24-hr urine Ca</td>
<td>To differentiate possible PHPT from HCHC</td>
</tr>
<tr>
<td>2016 AAES</td>
<td>HPT</td>
<td>IPM</td>
<td>Use IPM for parathyroidectomy</td>
</tr>
<tr>
<td>2018 Int’l Consensus on PHP</td>
<td>PHP &amp; related disorders (See Note 1 following Coverage Criteria)</td>
<td>Serum PTH, Ca, P</td>
<td>At diagnosis and then every 6 months for children and at least once a year for adults EXCEPT for patients with paternal allele mutations on GNAS gene or for PDE4D gene mutation…for these, test only for diagnosis</td>
</tr>
<tr>
<td>2018 Int’l Consensus on PHP</td>
<td>PHP &amp; related disorders (See Note 1 following Coverage Criteria)</td>
<td>Serum PTH, Ca, P</td>
<td>Every 6 months for patients undergoing PTH resistance therapy</td>
</tr>
<tr>
<td>2018 Int’l Consensus on PHP</td>
<td>PHP &amp; related disorders (See Note 1 following Coverage Criteria)</td>
<td>Serum Ca</td>
<td>Frequent testing (more often than every 6 months) during acute illness or symptomatic, during acute growth phase, and during pregnancy/breastfeeding</td>
</tr>
<tr>
<td>2018 Int’l Consensus on PHP</td>
<td>PHP &amp; related disorders (See Note 1 following Coverage Criteria)</td>
<td>Serum P</td>
<td>During vitamin D therapy</td>
</tr>
<tr>
<td>2014 4th Int’l Workshop on PHPT</td>
<td>PHPT</td>
<td>Serum Ca, PTH</td>
<td>Annual testing</td>
</tr>
<tr>
<td>2014 4th Int’l Workshop on PHPT</td>
<td>PHPT</td>
<td>P, 24-hr urine Ca</td>
<td>List these tests in evaluation of patients with asymptomatic PHPT, but do not state frequency of testing</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>MEN1/MEN2</td>
<td>Serum Ca, PTH</td>
<td>Annually, also for post-operative follow-up of parathyroidectomy</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>ALL</td>
<td>P, serum Ca</td>
<td>As part of initial workup and to monitor osteonecrosis development; also check serum Ca if undergoing steroid therapy</td>
</tr>
<tr>
<td>----------</td>
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<td>-------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Systemic Light Chain Amyloidosis</td>
<td>Serum Ca, electrolytes</td>
<td>As part of initial workup</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>GCTB</td>
<td>Serum Ca, P, PTH</td>
<td>Routine “evolution” to exclude brown tumor of HPT</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Metastatic Breast Cancer</td>
<td>Serum Ca</td>
<td>As part of routine testing to monitor metastatic disease &amp; effectiveness of current therapy</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Metastatic Breast Cancer</td>
<td>Serum Ca, P, Mg</td>
<td>As part of initial evaluation prior to starting bisphosphonate treatment or subcutaneous denosumab; frequent measurement “is prudent” under those treatments as well</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>CLL/SLL</td>
<td>Serum Ca, P</td>
<td>Use these tests to monitor small-molecule inhibitor-induced TLS (see table within guidelines for detailed frequency)</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Esophageal/Esophagogastric Junction Cancers</td>
<td>Serum Ca</td>
<td>Consider testing, especially following esophagectomy, due to possible calcium deficiency</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Kidney Cancer</td>
<td>Serum Ca</td>
<td>Used as a predictor of survivor for patients on Temsirolimus, but do not state frequency of testing</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Multiple Myeloma</td>
<td>Serum Ca, electrolytes</td>
<td>In initial diagnostic workup</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Multiple Myeloma</td>
<td>Serum Ca</td>
<td>“Corrected” Ca is recommended as part of follow-up</td>
</tr>
<tr>
<td>Year</td>
<td>Organization</td>
<td>Disease</td>
<td>Test(s)</td>
</tr>
<tr>
<td>------</td>
<td>--------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Occult Primary Cancers</td>
<td>Serum Ca, electrolytes</td>
<td>In initial evaluation of suspected metastatic malignancy</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Prostate Cancer</td>
<td>Serum Ca</td>
<td>In monitoring denosumab therapy</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Prostate Cancer</td>
<td>P</td>
<td>Monthly basis (at least initially) during abiraterone or abiraterone/prednisone therapy</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>ATLL</td>
<td>Serum Ca, electrolytes</td>
<td>In initial workup</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>T-Cell Lymphomas</td>
<td>Serum Ca, P</td>
<td>To monitor for TLS</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>Medullary Thyroid Carcinoma</td>
<td>Serum Ca</td>
<td>Upon diagnosis</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>MEN2A/Familial medullary thyroid carcinoma</td>
<td>Serum Ca, PTH</td>
<td>As part of workup for patients who have codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations</td>
</tr>
<tr>
<td>2019 NCCN</td>
<td>MEN1/MEN2</td>
<td>Serum Ca, PTH</td>
<td>Annually, also for post-operative follow-up of parathyroidectomy</td>
</tr>
<tr>
<td>2012, 2017 KDIGO</td>
<td>CKD</td>
<td>Serum Ca, P, PTH</td>
<td>Look at detailed frequency tables within the guidelines section for frequency of testing</td>
</tr>
<tr>
<td>2013 AUA</td>
<td>Renal Neoplasms</td>
<td>Serum Ca</td>
<td>Testing to be used at the clinician’s discretion</td>
</tr>
<tr>
<td>2014 AUA</td>
<td>Kidney Stones</td>
<td>Intact PTH</td>
<td>In screening if suspected HPT</td>
</tr>
<tr>
<td>2014 AUA</td>
<td>Kidney Stones</td>
<td>24-hr urine Ca</td>
<td>Test one or two collections, but do not use “fast and calcium load” testing to distinguish hypercalciuria</td>
</tr>
<tr>
<td>2013 NICE</td>
<td>CKD (stage 4 or 5)</td>
<td>Serum Ca, PTH, P</td>
<td>Do not state frequency of testing but stress testing results for determining therapy to be used</td>
</tr>
<tr>
<td>2014 NICE</td>
<td>CKD</td>
<td>Serum Ca, PTH, P</td>
<td>Do not routinely measure in patients with category G1, G2, or G3 CKD</td>
</tr>
<tr>
<td>Year</td>
<td>Indication</td>
<td>Test(s)</td>
<td>Recommendation</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------</td>
<td>------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2014 NICE</td>
<td>CKD</td>
<td>Serum Ca, PTH, P</td>
<td>Do measure in patients with category G4 or G5 CKD</td>
</tr>
<tr>
<td>2014 NICE</td>
<td>CKD</td>
<td>Serum Ca, P</td>
<td>Monitor in patients on alfacalcidol or calcitriol</td>
</tr>
<tr>
<td>2014 NICE</td>
<td>Bipolar disorder</td>
<td>Serum Ca, electrolytes</td>
<td>Initial screening prior to lithium therapy; every six months (more often if impaired renal or thyroid function)</td>
</tr>
<tr>
<td>2014 NICE</td>
<td>MS</td>
<td>Serum Ca</td>
<td>Prior to referring patient with suspected MS to neurologist</td>
</tr>
<tr>
<td>2015 NICE</td>
<td>Suspected Cancer</td>
<td>Serum Ca</td>
<td>For diagnosis of possible myeloma in anyone 60 years or older with persistent bone pain or unexplained fracture</td>
</tr>
<tr>
<td>2019 NICE</td>
<td>Chronic Kidney Disease</td>
<td>P</td>
<td>Should be considered before any education on kidney replacement treatment begins</td>
</tr>
<tr>
<td>2017 ASCO/CCO</td>
<td>Breast Cancer</td>
<td>Serum Ca</td>
<td>Prior to starting treatment with bisphosphonates and test to monitor renal function during treatment</td>
</tr>
<tr>
<td>2014 SOGC</td>
<td>Hypertensive Disorders During Pregnancy</td>
<td>Serum Mg</td>
<td>Do NOT recommend routine monitoring</td>
</tr>
<tr>
<td>2013 ICSI</td>
<td>Adult Heart Failure</td>
<td>Serum Ca, Mg</td>
<td>Prior to initiating loop thiazide diuretics and then every four months during therapy</td>
</tr>
<tr>
<td>2016 AACE/ACE</td>
<td>Osteoporosis</td>
<td>Intact PTH, 24-hr urine Ca, P</td>
<td>Recommended to assess for possible causation of secondary osteoporosis</td>
</tr>
<tr>
<td>2016 AAP</td>
<td>BRUE</td>
<td>Serum Ca</td>
<td>NOT recommended for use on infants less than 1-yr old presenting with a lower-risk BRUE</td>
</tr>
<tr>
<td>2013 AACE/ACE/TOS</td>
<td>CKD</td>
<td>Intact PTH</td>
<td>Recommended testing but does not discuss frequency</td>
</tr>
<tr>
<td>2013 AACE/ACE/TOS</td>
<td>CKD</td>
<td>24-hr urine Ca</td>
<td>Recommended for CKD patients with osteoporosis</td>
</tr>
</tbody>
</table>
### Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing

**AHS – G2164**

<table>
<thead>
<tr>
<th>Year</th>
<th>Society</th>
<th>Indication</th>
<th>Test(s)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>AACE/ACE/TOS</td>
<td>CKD</td>
<td>Serum Ca, P</td>
<td>Recommended for CKD patients during vitamin D therapy</td>
</tr>
<tr>
<td>2013</td>
<td>AACE/TOS/ASM BS</td>
<td>Bariatric Surgery &amp; Osteoporosis</td>
<td>Serum Ca (total), P, PTH, 24-hr urine Ca</td>
<td>For osteoporosis patients undergoing bariatric surgery who undergo bisphosphonate therapy</td>
</tr>
<tr>
<td>2019</td>
<td>AACE/TOS/ASM BS</td>
<td>Women Who Become Pregnant After a Bariatric Procedure</td>
<td>Ca</td>
<td>Should be tested every trimester</td>
</tr>
<tr>
<td>2019</td>
<td>AACE/TOS/ASM BS</td>
<td>Bariatric Procedures</td>
<td>Serum PTH, Ca, P, Urine Ca</td>
<td>May be tested for during an evaluation for bone loss after bariatric procedures</td>
</tr>
<tr>
<td>2013 AGA</td>
<td></td>
<td>Constipation</td>
<td>Serum Ca</td>
<td>NOT recommended for chronic constipation</td>
</tr>
<tr>
<td>2015 National Blood Authority</td>
<td></td>
<td>Obstetric Hemorrhage</td>
<td>Ionized Serum Ca</td>
<td>Recommended to be measured early and frequently</td>
</tr>
<tr>
<td>2016 ATA</td>
<td></td>
<td>Thyroidectomy for Toxic Multinodular Goiter</td>
<td>Serum Ca, intact PTH</td>
<td>Serum Ca should be measured with or without intact PTH</td>
</tr>
<tr>
<td>2016 ATA</td>
<td></td>
<td>Graves’ Disease Patients Undergoing a Thyroidectomy</td>
<td>Ca</td>
<td>Should be assessed preoperatively</td>
</tr>
</tbody>
</table>

**Abbreviations (not including Society acronyms):**
- ALL = acute lymphoblastic leukemia
- ATLL = adult T-Cell Leukemia/Lymphoma
- BRUE = Brief Resolved Unexplained Events in infants
- Ca = calcium testing
- CKD = chronic kidney disease
- CLL = chronic lymphocytic leukemia
- GCTB = Giant Cell Tumor of Bone
- HCHC = hypocalciuric hypercalcemia
- HPT = hyperparathyroidism (non-specific)
- IPM = intraoperative PTH monitoring
- MEN1 = Multiple Endocrine Neoplasia, Type 1
- MEN2 = Multiple Endocrine Neoplasia, Type 2
- Mg = magnesium testing
- MS = Multiple Sclerosis
- P = phosphorus/phosphate testing
- PHP = pseudoparathyroidism
- PHPT = primary hyperparathyroidism
- PTH = parathyroid hormone
- SLL = small lymphocytic lymphoma
- TLS = Tumor Lysis Syndrome

### 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:** 82310, 82330, 82340, 83735, 83970, 84100, 84105

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.
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Policy Implementation/Update Information

5/14/19 New policy developed. BCBSNC will provide coverage for Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 4/1/2019. Policy noticed 5/14/2019 for effective date 7/16/2019. (an)

10/1/19 Policy statement revised to read: BCBSNC will provide coverage for Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing when it is determined the medical criteria or reimbursement guidelines below are met. Wording revised in When Covered section. “Medically Necessary” changed to “Reimbursement is allowed…” Wording revised in the Not Covered section. “Not Medically Necessary” and “Investigational” changed to read “Reimbursement is not allowed…” Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)

5/12/20 Background, Policy Guidelines, and Reference sections updated. Reviewed by Avalon for 1st Quarter 2020 CAB. No change to policy statement. Medical Director review 4/2020. (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.