Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing

Policy Number: AHS – G2164 – Parathyroid Hormone, Phosphorus, Calcium, and Magnesium Testing	Prior Policy Name and Number, as applicable:
Original Effective Date: 5/15/2022 Current Effective Date: 5/15/2022	

I. Policy Description

Parathyroid hormone (PTH), along with calcitriol and fibroblast growth factor 23 (FGF23), 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, 2019)."

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, 2019). 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, 2020).

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, 2019).

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)."

II. Related Policies

Policy Number	Policy Title
AHS-G2005	Vitamin D Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

1. Serum intact parathyroid (PTH) testing **MEETS COVERAGE CRITERIA** 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. Serum intact parathyroid (PTH) testing in cases of possible hypoparathyroidism, pseudohypoparathyroidism, or related disorders* (See Note 1) **MEETS COVERAGE CRITERIA** 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.
3. Serum intact parathyroid (PTH) testing **DOES NOT MEET COVERAGE CRITERIA** in screening of patients for asymptomatic hyperparathyroidism.

4. The following tests **DO NOT MEET COVERAGE CRITERIA** for individuals in general encounters without abnormal findings or wellness visits:

    a. Serum, blood, or fecal magnesium testing

    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

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

5. Testing serum for truncated parathyroid hormone metabolites, including amino-terminal and carboxy-terminal fragments, **DOES NOT MEET COVERAGE CRITERIA**.

*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*

IV. Scientific 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, 2019). The bar graph figure below is taken from Valcour et al. (2018), and 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, 2020; Valcour et al., 2018).

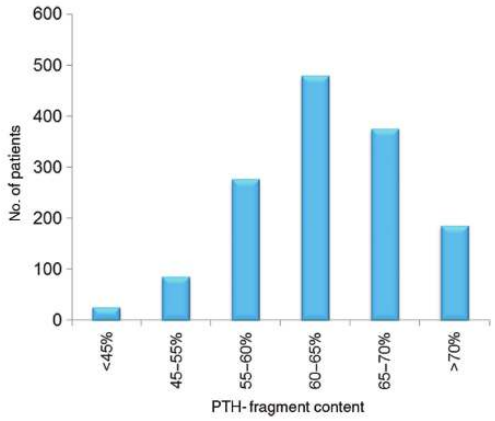

Figure 4: Frequency of fragment content in hemodialysis patients. Representative PTH fragment was assessed in 1533 hemodialysis samples by measuring both PTH(1-84) with the LIAISON method, and iPTH with Method A (high cross-reactivity with inactive fragments [4]). The fragment content was calculated as (iPTH-PTH(1-84))/iPTH and expressed as % of total iPTH.

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 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 bloodstream 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 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 hypophosphatemia, 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 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). This extensive review covered everything from circadian rhythms and how time of day affected clinical validity to storage conditions and seasonal changes. The research included data from 83 different studies. The authors 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 it is noted that "PTH has a circadian rhythm characterized by a nocturnal acrophase and mid-morning nadir (Hanon et al., 2013)." The data was found to be contradictory concerning the validity of results obtained from frozen samples regardless of whether the sample was stored at -20°C or -80°C. PTH concentrations were also considerably higher in central blood as compared to peripheral blood (median values of 24.3 pmol/L versus 15.3 pmol/L, respectively). It is recommended 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.

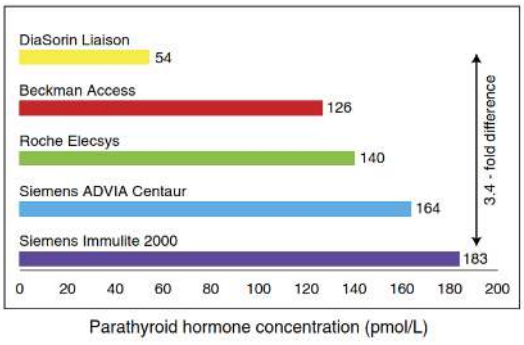

Figure 1 Between-method differences in the concentration of parathyroid hormone (PTH) observed in a typical single patient specimen

The study by 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 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 et al. (2018) evaluated the efficacy of the LIAISON 1-84 PTH test, a third-generation serum test, as compared to other intact testing methods. This 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. Each test's efficacy was also evaluated 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). Two different standards were used—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 (Valcour et al., 2018)." 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…."; The authors 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 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, Willett, Speizer, and 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. Samples were collected 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 ($p \leq 0.01$) 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. Conclusions state 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, 2018b). The evidence of causation or the use of serum magnesium in predicting preeclampsia have been inconclusive. A study by Kreepala, Kitporntheranunt, Sangwipasnapaporn, Rungsrithananon, and Wattanavaekin (2018) has proposed the use of serum total magnesium and ionized magnesium levels to develop a magnesium-based equation for screening of preeclampsia. This study involved 84 pregnant women including 20 controls. The remaining 64 had been diagnosed with preeclampsia after the 20th week of pregnancy. The authors 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 that was 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." Kreepala et al. (2018) 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."

Serum magnesium levels have been identified to play a role in other disorders as well. Low serum magnesium levels have recently been associated with a greater coronary artery disease risk Hamedanian, Badehnoosh, Razavi-Khorasani, Mohammadpour, and Mozaffari-Khosravi (2019); (Rooney et al., 2020). A total of 14446 participants were followed for one year in a large meta-analysis study. The researchers concluded that "low circulating Mg was associated with higher CAD risk than was higher Mg"; however, it was not determined whether magnesium concentration manipulation could assist in the prevention of coronary artery disease (Rooney et al., 2020).

V. Guidelines and Recommendations

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

The AAES released guidelines concerning primary hyperparathyroidism (pHPT) in 2016. With respect to laboratory testing, in Recommendation 1-1, these guidelines state, "The biochemical evaluation of suspected pHPT should include serum total calcium, PTH, creatinine, and 25-hydroxyvitamin D levels (strong recommendation; moderate-quality evidence)." The AAES also addresses 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." The AAES 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, a strong recommendation with low-quality evidence to recommendation 6-2 was provided: "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." The frequency of testing either calcium or PTH post-operatively is not given, but the AAES mentions these recommendations in several comments concerning the 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). It is also stated 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 Pseudohypoparathyroidism 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 pseudohypoparathyroidism 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). Pseudohypoparathyroidism can be classified as either type 1A or 1B (PHP1A and PHP1B, respectively), depending on the type of defect in the *GNAS* coding sequence. Pseudopseudohypoparathyroidism (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+++), the guidelines 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, the measurement of serum PTH, calcium, phosphorus, and calcifediol are recommended; 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++), the guidelines 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+), the routine measurement of calcitonin is not recommend.

2020 European Network on Pseudohypoparathyroidism (EuroPHPnet) (Mantovani et al., 2020)

The EuroPHPnet published its "Recommendations for Diagnosis and Treatment of Pseudohypoparathyroidism and Related Disorders: an Updated Practice Tool for Physicians and Patients". In these guidelines, the EuroPHPnet noted that "PTH resistance is the hallmark of PHP [pseudohypoparathyroidism], found in 45-80% of patients", and symptoms of PTH resistance should not be ignored and "screening and follow-up of PTH resistance should include measurement of PTH, 25-OH vitamin D, calcium, and phosphate every 3-6 months in children and at least yearly in adults." However, the frequency of monitoring is also contingent on whether the individual is symptomatic or not, in acute phases of growth, experiencing intercurrent illness, pregnancy, or is breastfeeding. In the case of pregnant women with hypocalcemia and/or hypothyroidism, they "should be monitored following the international guidelines for any pregnancy associated with these disturbances" and their newborns "should be evaluated for the presence of skin ossifications and levels of TSH, calcium, and phosphorous" (Mantovani et al., 2020).

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. A formula is given to determine corrected calcium concentration, which is recommend rather than using 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)]

The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism list their recommendations for evaluating asymptomatic PHPT in Table 3 shown below although the guidelines 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 3. Recommendations for the Evaluation of Patients With Asymptomatic PHPT

Recommended
Biochemistry panel (calcium, phosphate, alkaline phosphatase activity, BUN, creatinine), 25(OH)D
PTH by second- or third-generation immunoassay
BMD by DXA
Lumbar spine, hip, and distal 1/3 radius
Vertebral spine assessment
X-ray or VFA by DXA
24-h urine for:
Calcium, creatinine, creatinine clearance
Stone risk profile
Abdominal imaging by x-ray, ultrasound, or CT scan
Optional
HRpQCT
TBS by DXA
Bone turnover markers (bone-specific alkaline phosphatase activity, osteocalcin, P1NP [select one]; serum CTX, urinary NTX [select one])
Fractional excretion of calcium on timed urine sample
DNA testing if genetic basis for PHPT is suspected

Abbreviations: BUN, blood urea nitrogen; P1NP, procollagen type 1 N-propeptide; CTX, C-telopeptide cross-linked collagen type I; NTX, N-telopeptide of type I collagen. This evaluation is for PHPT, not to distinguish between PHPT and other causes of hypercalcemia.

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

National Comprehensive Cancer Network (NCCN)

The NCCN addresses PTH, calcium, phosphate, and magnesium testing in several different guidelines.

Neuroendocrine & Adrenal Tumors (NCCN, 2020h): The NCCN continues to assert that "Primary hyperparathyroidism associated with parathyroid adenomas is the most common manifestation of MEN1. Measurement of serum calcium levels and parathyroid hormone (PTH) is recommended if hyperparathyroidism is suspected." However, in version 2 of the

2020 NCCN guidelines regarding this topic, the NCCN revised their previous guidelines. In the section concerning Multiple Endocrine Neoplasia, Type 1 (MEN1), the NCCN proposes the use of serum calcium in the diagnosis and clinical evaluation of suspected MEN1, and in the instance that calcium levels are elevated PTH and 25-OH vitamin D be explored. Explicitly, for the evaluation of parathyroid tumors in MEN1, the NCCN states that "Measurement of serum calcium levels is recommended if hyperparathyroidism is suspected. If calcium levels are elevated, parathyroid hormone (PTH) and 25-OH vitamin D levels should be checked." With respect to the surveillance of MEN1-associated parathyroid tumors, "The panel recommends annual calcium and serum PTH levels to be screened for parathyroid tumors. If calcium levels rise, 25-OH vitamin D should be measured and imaging with neck ultrasound and/or parathyroid sestamibi with SPECT scan or 4D-CT should be performed." Similarly, for the evaluation of patients with Multiple Endocrine Neoplasia Type 2 (MEN2), "serum calcium levels should be measured. If it is found to be elevated, PTH and 25-OH vitamin D levels should be measured. A neck ultrasound, sestamibi scan with SPECT, or 4D-CT scan can also be performed as appropriate." The NCCN continues to recommend the use of "calcium, PTH, calcitonin, and metanephrine levels be evaluated to screen for parathyroid tumors" following a subtotal or total parathyroidectomy, with emphasis on calcium annually for surveillance.

Acute Lymphoblastic Leukemia (ALL): As part of the initial workup for ALL patients, they recommend "a tumor lysis syndrome (TLS) 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 guidelines 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. Likewise, the NCCN later stated "To monitor patients for risks of developing symptomatic osteonecrosis, routine measurements for vitamin D and calcium levels should be used (NCCN, 2020a)."

Systemic Light Chain Amyloidosis: As part of the initial diagnostic workup, in the section titled "Laboratory evaluation (directed toward commonly affected organ systems)," the NCCN recommends testing "serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid, serum LDH, and beta-2 microglobulin (NCCN, 2020k)."

Bone Cancer (NCCN, 2020b) In the section concerning the workup of Giant Cell Tumor of Bone (GCTB), a rare benign tumor, the guidelines state that "brown tumor of hyperparathyroidism should be considered as a differential diagnosis; routine evolution of serum calcium, phosphate, and parathyroid hormone levels can help exclude this diagnosis (NCCN, 2018a, 2019, 2020b)." Moreover, prior to treatment of bone lesions, it is recommended that "Laboratory studies, such as…calcium to assess for hypercalcemia, should be done prior to initiation of treatment" (NCCN, 2020b, 2020g).

Breast Cancer (NCCN, 2021a): 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 (NCCN, 2018b, 2021a)."

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): 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 note that "patients with bulky lymph nodes, progressive disease after small-molecular inhibitor therapy, and receiving chemotherapy, venetoclax, lenalidomide, obintuzumab are considered to be at high-risk for TLS." NCCN further states that hallmarks of TLS include high potassium, uric acid, phosphorous, lactate dehydrogenase, and low calcium. 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 the guideline) depicts the blood chemistry monitoring as recommended:

Blood Chemistry Monitoring (potassium uric acid, phosphorus, calcium and creatinine)	
Low Tumor Burden	
Outpatient setting	Pre-dose 6-8 hrs after dose 24 hrs at first dose of 20-50 mg
Medium Tumor Burden	
Outpatient setting	Pre-dose 6-8 hrs after dose 24 hrs at first dose of 20-50 mg Pre-dose at subsequent ramp-up doses Consider hospitalization for patients with CrCl <80 mL/min at first dose of 20 mg and 50 mg
High Tumor Burden	
In hospital setting	At first dose of 20-50 mg Pre-dose 4 hrs 8 hrs 12 hrs 24 hrs
Outpatient setting (for subsequent ramp-up doses)	Pre-dose 6-8 hrs 24 hrs

Special considerations are asked to be made for the use of small-molecule inhibitors, such that "tumor burdens assessments, including CT scan and blood chemistry (potassium, uric acid, phosphorous, calcium, and creatinine) in all patients" should be performed prior to treatment with venetoclax due to reduced renal function increasing the risk of TLS (NCCN, 2020a).

Esophageal and Esophagogastric Junction Cancers: 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 B_{12}, folic acid, and vitamin D (NCCN, 2020c)

Kidney Cancer: 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)"]. The guidelines do not state how frequently serum calcium should be tested or if it is solely for use at diagnosis. However, the guidelines recommend that laboratory evaluation for patients with renal cell carcinoma typically present with a suspicious mass involving the kidney may include a metabolic panel consisting of "corrected calcium, serum creatinine, liver function studies, and urinalysis" (NCCN, 2020d).

Multiple Myeloma (NCCN, 2020e): In the initial diagnostic workup for multiple myeloma, the NCCN recommends testing "serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid, serum LDH, and beta-2 microglobulin (NCCN, 2020f)." As follow-up to the clinical presentation of either "solitary plasmocytoma" (with minimal marrow involvement or less) 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 bone disease can lead to excessive release of calcium into the blood, contributing to hypercalcemia" (NCCN, 2020e, 2020f).

Occult Primary (Cancer of Unknown Primary [CUP]): "Routine laboratory tests (ie, complete blood count [CBC], electrolytes, liver function tests, creatinine, calcium…)are also recommended." (NCCN, 2020i)

Prostate Cancer: In the section concerning the treatment with denosumab, the guidelines 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 (NCCN, 2018c, 2020j)." In the section concerning patients with castration resistant prostate cancer (CRPC), the NCCN states, "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 is warranted during abiraterone therapy." Men with

CRPC are at a higher risk for severe hypocalcemia and hypophosphatemia due to use of denosumab (NCCN, 2021b)

T-Cell Lymphomas: 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, the NCCN recommends monitoring for tumor lysis syndrome (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" (NCCN, 2020l).

Thyroid Carcinoma: 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 (NCCN, 2020m).

2012, 2017 Kidney Disease Improving Global Outcomes (KDIGO) (KDIGO, 2013, 2017; Ketteler et al., 2017)

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 m^2 (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":

CKD Stage	Test	Reasonable Monitoring Interval
G3a-G3b	Serum Calcium	Every 6-12 months
G3a-G3b	Serum Phosphate	Every 6-12 months
G3a-G3b	PTH	"Based on baseline level and CKD progression"
G4	Serum Calcium	Every 3-6 months
G4	Serum Phosphate	Every 3-6 months
G4	PTH	Every 6-12 months
G5	Serum Calcium	Every 1-3 months
G5	Serum Phosphate	Every 1-3 months
G5	PTH	Every 3-6 months
G4-G5D	Alkaline Phosphatase Activity	Every 12 months, or more frequently in the presence of elevated PTH

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:

CKD Stage	Test	Reasonable Monitoring Interval
G1T-G3bT	Serum Calcium	Every 6-12 months
G1T-G3bT	Serum Phosphate	Every 6-12 months
G1T-G3bT	PTH	Once, with subsequent intervals depending on

CKD Stage	Test	Reasonable Monitoring Interval
		baseline level and CKD progression
G4T	Serum Calcium	Every 3-6 months
G4T	Serum Phosphate	Every 3-6 months
G4T	PTH	Every 6-12 months
G5T	Serum Calcium	Every 1-3 months
G5T	Serum Phosphate	Every 1-3 months
G5T	PTH	Every 3-6 months
G3aT-G5T	Alkaline Phosphatase Activity	Annually, or more frequently in the presence of elevated PTH

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)."

American Urological Association (AUA) (Donat et al., 2013; Pearle et al., 2019; M. Pearle et al., 2014)

In 2013, the AUA published *Follow-up for Clinically Localized Renal Neoplasms*. In recommendation 2, as an *Expert Opinion*, the AUA states, "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. These guidelines were reviewed, and validity was confirmed in 2019 (Pearle et al., 2019). In recommendation 2, the AUA recommends that "clinicians should obtain serum intact parathyroid hormone (PTH) level as part of the screening evaluation if primary hyperparathyroidism is suspected." Also recommend (Recommendations 6 & 7) is 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 (M. Pearle et al., 2014)."

2013-2019 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 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.

2014 Chronic kidney disease in adults: assessment and management (NICE, 2014b): In recommendation 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 m^2 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, 2014a, 2014c): 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 B_{12}, 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."

2019 Clinical practice guideline: undernutrition in chronic kidney disease (Wright, Southcott, MacLaughlin, & Wineberg, 2019): These guidelines include a section regarding the nutritional status of an individual with chronic kidney disease. The NICE states that "Assessment of nutritional status should therefore be considered when patients begin education for kidney replacement treatment as part of their overall care as well as for potential intervention regarding salt, potassium, phosphate and protein / energy intake assessments (Wright et al., 2019)." Specific assessment methods are not mentioned.

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."

American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) (Camacho et al., 2016)

In 2016, the AACE/ACE posted guidelines concerning osteoporosis in post-menopausal women recommending PTH, phosphate, and 24-hour urine calcium testing in evaluating osteoporosis. The guidelines 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 (Camacho et al., 2016)."

In the 2017 guidelines for the management of dyslipidemia prevention of cardiovascular disease, the AACE/ACE highlighted the use of coronary artery calcium scores in the detection of cardiovascular risk, stating that coronary artery calcium scoring "is recognized by the AHA as a surrogate marker for coronary heart disease" (Jellinger et al., 2017)

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 recommend using magnesium supplements for pregnant women; however, the SOGC clearly states in recommendation #120 that "routine monitoring of serum magnesium levels is not recommended (Magee et al., 2014)."

2013 Institute for Clinical Systems Improvement (ICSI) (NGC, 2013)

In the ICSI's guidelines concerning adult heart failure, both magnesium and calcium testing for patients undergoing loop thiazide diuretics are recommended with a frequency of "before diuretic initiation, then every four months for the duration of therapy (NGC, 2013)."

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), the AAP states 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) (Tieder et al., 2016)."

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, 2019 AACE/TOS/ASMBS (American Society for Metabolic & Bariatric Surgery)/OMA (Obesity Medical Association)/ASA (American Society of Anesthesiologists) (Mechanick et al., 2019; Mechanick et al., 2013)

Also, in 2013, the AACE/TOS/ASMBS/OMA/ASA 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)."

The updated guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures were published by the ACE, TOS, ASMBS as well as the Obesity Medicine Association, and the American Society of Anesthesiologists Boards of Directors. The guidelines give the following recommendations:

- "Patients who become pregnant following bariatric procedure should have nutritional surveillance and laboratory screening for nutrient deficiencies every trimester, including iron, folate, vitamin B12, vitamin D, and calcium, and if after a malabsorptive procedure, fat-soluble vitamins, zinc, and copper (Grade D)
- Evaluation of patients for bone loss after bariatric procedures may include serum parathyroid hormone, total calcium, phosphorus, 25-hydroxyvitamin D, and 24-hour urine calcium levels (Grade C; BEL 3) (Mechanick et al., 2019)."

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)."

American Thyroid Association (ATA) (Orloff et al., 2018; Ross et al., 2016)

The ATA has published guidelines for the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. The ATA has stated that after a thyroidectomy, "serum calcium with or without intact parathyroid hormone (iPTH) levels can be measured,"; further, after a thyroidectomy for TMNG (toxic multinodular goiter), "serum calcium with or without iPTH

levels should be measured" (Ross et al., 2016). When preparing patients with GD (Graves' disease) for a thyroidectomy, the ATA recommends that "Calcium and 25-hydroxy vitamin D should be assessed preoperatively and repleted if necessary (Ross et al., 2016)."

The ATA also published a statement regarding postoperative hypoparathyroidism. In it, they recommend to "Either treat at-risk patients empirically with calcium, or measure calcium and/or PTH in the immediate postoperative period and treat according to evidence-based protocols." (Orloff et al., 2018)

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 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."

The guidelines and recommendations are summarized in the table given below:

Year & Society	Condition	Test	Recommendation
2016 AAES	PHPT	Serum Ca, PTH	Testing in evaluation of suspected PHPT; test at least one, if not both, six months post-parathyroidectomy
2016 AAES	PHPT/HCHC	24-hr urine Ca	To differentiate possible PHPT from HCHC
2016 AAES	HPT	IPM	Use IPM for parathyroidectomy
2018 Int'l Consensus on PHP	PHP & related disorders (See Note 1 following Coverage Criteria)	Serum PTH, Ca, P	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
2018 Int'l Consensus on PHP	PHP & related disorders (See Note 1 following Coverage Criteria)	Serum PTH, Ca, P	Every 6 months for patients undergoing PTH resistance therapy
2018 Int'l Consensus on PHP	PHP & related disorders (See Note 1 following Coverage Criteria)	Serum Ca	Frequent testing (more often than every 6 months) during acute illness or symptomatic, during acute growth phase, and during pregnancy/breastfeeding
2018 Int'l Consensus on PHP	PHP & related disorders (See Note 1 following Coverage Criteria)	Serum P	During vitamin D therapy
2014 4th Int'l Workshop on PHPT	PHPT	Serum Ca, PTH	Annual testing
2014 4th Int'l Workshop on PHPT	PHPT	P, 24-hr urine Ca	List these tests in evaluation of patients with asymptomatic PHPT, but do not state frequency of testing
2020 NCCN	MEN1/MEN2	Serum Ca, PTH	Annually, also for post-operative follow-up of parathyroidectomy
2020 NCCN	ALL	P, serum Ca	As part of initial workup and to monitor osteonecrosis development; also

			check serum Ca if undergoing steroid therapy
2020 NCCN	Systemic Light Chain Amyloidosis	Serum Ca, electrolytes	As part of initial workup
2020 NCCN	GCTB	Serum Ca, P, PTH	Routine "evolution" to exclude brown tumor of HPT
2020 NCCN	Metastatic Breast Cancer	Serum Ca	As part of routine testing to monitor metastatic disease & effectiveness of current therapy
2020 NCCN	Metastatic Breast Cancer	Serum Ca, P, Mg	As part of initial evaluation prior to starting bisphosphonate treatment or subcutaneous denosumab; frequent measurement "is prudent" under those treatments as well
2020 NCCN	CLL/SLL	Serum Ca, P	Use these tests to monitor small-molecule inhibitor-induced TLS (see table within guidelines for detailed frequency)
2020 NCCN	Esophageal/Esophagogastric Junction Cancers	Serum Ca	Consider testing, especially following esophagectomy,

			due to possible calcium deficiency
2020 NCCN	Kidney Cancer	Serum Ca	Used as a predictor of survivor for patients on Temsirolimus, but do not state frequency of testing
2020 NCCN	Multiple Myeloma	Serum Ca, electrolytes	In initial diagnostic workup
2020 NCCN	Multiple Myeloma	Serum Ca	"Corrected" Ca is recommended as part of follow-up
2020 NCCN	Occult Primary Cancers	Serum Ca, electrolytes	In initial evaluation of suspected metastatic malignancy
2020 NCCN	Prostate Cancer	Serum Ca	In monitoring denosumab therapy
2020 NCCN	Prostate Cancer	P	Monthly basis (at least initially) during abiraterone or abiraterone/prednisone therapy
2020 NCCN	ATLL	Serum Ca, electrolytes	In initial workup
2020 NCCN	T-Cell Lymphomas	Serum Ca, P	To monitor for TLS
2020 NCCN	Medullary Thyroid Carcinoma	Serum Ca	Upon diagnosis
2020 NCCN	MEN2A/Familial medullary thyroid carcinoma	Serum Ca, PTH	As part of workup for patients who have codon 609, 611, 618, 620, 630,

			634, 768, 790, 791, 804, or 891 RET mutations
2012, 2017 KDIGO	CKD	Serum Ca, P, PTH	Look at detailed frequency tables within the guidelines section for frequency of testing
2013,2019 AUA	Renal Neoplasms	Serum Ca	Testing to be used at the clinician's discretion
2014 AUA	Kidney Stones	Intact PTH	In screening if suspected HPT
2014 AUA	Kidney Stones	24-hr urine Ca	Test one or two collections, but do not use "fast and calcium load" testing to distinguish hypercalciuria
2013 NICE	CKD (stage 4 or 5)	Serum Ca, PTH, P	Do not state frequency of testing but stress testing results for determining therapy to be used
2014 NICE	CKD	Serum Ca, PTH, P	Do not routinely measure in patients with category G1, G2, or G3 CKD
2014 NICE	CKD	Serum Ca, PTH, P	Do measure in patients with category G4 or G5 CKD

2014 NICE	CKD	Serum Ca, P	Monitor in patients on alfacalcidol or calcitriol
2014 NICE	Bipolar disorder	Serum Ca, electrolytes	Initial screening prior to lithium therapy; every six months (more often if impaired renal or thyroid function)
2014 NICE	MS	Serum Ca	Prior to referring patient with suspected MS to neurologist
2015 NICE	Suspected Cancer	Serum Ca	For diagnosis of possible myeloma in anyone 60 years or older with persistent bone pain or unexplained fracture
2019 NICE	Chronic Kidney Disease	P	Should be considered before any education on kidney replacement treatment begins
2017 ASCO/CCO	Breast Cancer	Serum Ca	Prior to starting treatment with bisphosphonates and test to monitor renal function during treatment
2014 SOGC	Hypertensive Disorders During Pregnancy	Serum Mg	Do NOT recommend routine monitoring
2013 ICSI	Adult Heart Failure	Serum Ca, Mg	Prior to initiating loop thiazide diuretics and then

			every four months during therapy
2016 AACE/ACE	Osteoporosis	Intact PTH, 24-hr urine Ca, P	Recommended to assess for possible causation of secondary osteoporosis
2016 AAP	BRUE	Serum Ca	NOT recommended for use on infants less than 1-yr old presenting with a lower-risk BRUE
2013 AACE/ACE/TOS	CKD	Intact PTH	Recommended testing but does not discuss frequency
2013 AACE/ACE/TOS	CKD	24-hr urine Ca	Recommended for CKD patients with osteoporosis
2013 AACE/ACE/TOS	CKD	Serum Ca, P	Recommended for CKD patients during vitamin D therapy
2013 AACE/TOS/ASMBS	Bariatric Surgery & Osteoporosis	Serum Ca (total), P, PTH, 24-hr urine Ca	For osteoporosis patients undergoing bariatric surgery who undergo bisphosphonate therapy
2019 AACE/TOS/ASMBS	Women Who Become Pregnant After a Bariatric Procedure	Ca	Should be tested every trimester
2019 AACE/TOS/ASMBS	Bariatric Procedures	Serum PTH, Ca, P, Urine Ca	May be tested for during an evaluation for bone loss after bariatric procedures

2013 AGA	Constipation	Serum Ca	NOT recommended for chronic constipation
2015 National Blood Authority	Obstetric Hemorrhage	Ionized Serum Ca	Recommended to be measured early and frequently
2016 ATA	Thyroidectomy	Serum Ca, intact PTH	Serum Ca can be measured with or without intact PTH
2016 ATA	Thyroidectomy for Toxic Multinodular Goiter	Serum Ca, intact PTH	Serum Ca should be measured with or without intact PTH
2016 ATA	Graves' Disease Patients Undergoing a Thyroidectomy	Ca	Should be assessed preoperatively

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

VI. State and Federal Regulations, as applicable

The FDA has approved many different tests and assays for parathyroid hormone. A search of the FDA Device Database on 1/15/2021 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 1/15/2021. An FDA database search using "magnesium test" as search criteria yielded fourteen different FDA-approved tests (FDA, 2021).

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.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
82310	Calcium; total
82330	Calcium; ionized
82340	Calcium; urine quantitative, timed specimen
83735	Magnesium
83970	Parathormone (parathyroid hormone)
84100	Phosphorus inorganic (phosphate)
84105	Phosphorus inorganic (phosphate); urine

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

AACC. (2013, 12/12/2013). Phosphorus. *Lab Tests Online.* Retrieved from https://labtestsonline.org/tests/phosphorus

AACC. (2014, 03/07/2014). Calcium. *Lab Tests Online.* Retrieved from https://labtestsonline.org/tests/calcium

AACC. (2017, 06/29/2017). Magnesium. *Lab Tests Online.* Retrieved from https://labtestsonline.org/tests/magnesium

Almond, A., Ellis, A. R., & Walker, S. W. (2012). Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease. *Ann Clin Biochem, 49*(Pt 1), 63-67. doi:10.1258/acb.2011.011094

Bensalah, M., Bouayadi, O., Rahmani, N., Lyagoubi, A., Lamrabat, S., & Choukri, M. (2018). Comparative study of the serum measurement of PTH on Roche Cobas e411((R)) versus the Abbott Architect ci8200((R)). *Ann Biol Clin (Paris), 76*(1), 61-67. doi:10.1684/abc.2017.1309

Bharucha, A. E., Dorn, S. D., Lembo, A., & Pressman, A. (2013). American Gastroenterological Association medical position statement on constipation. *Gastroenterology, 144*(1), 211-217. doi:10.1053/j.gastro.2012.10.029

Bilezikian, J. P., Brandi, M. L., Eastell, R., Silverberg, S. J., Udelsman, R., Marcocci, C., & Potts, J. J. T. (2014). Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. *The Journal of Clinical Endocrinology & Metabolism, 99*(10), 3561-3569. doi:10.1210/jc.2014-1413

Bislev, L. S., Langagergaard Rodbro, L., Sikjaer, T., & Rejnmark, L. (2019). Effects of Elevated Parathyroid Hormone Levels on Muscle Health, Postural Stability and Quality of Life in Vitamin D-Insufficient Healthy Women: A Cross-Sectional Study. *Calcif Tissue Int, 105*(6), 642-650. doi:10.1007/s00223-019-00612-2

Camacho, P. M., Petak, S. M., Binkley, N., Clarke, B. L., Harris, S. T., Hurley, D. L., . . . Watts, N. B. (2016). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016. *Endocr Pract, 22*(Suppl 4), 1-42. doi:10.4158/ep161435.Gl

Curhan, G. C., Willett, W. C., Speizer, F. E., & Stampfer, M. J. (2001). Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int, 59*(6), 2290-2298. doi:10.1046/j.1523-1755.2001.00746.x

Dhesy-Thind, S., Fletcher, G. G., Blanchette, P. S., Clemons, M. J., Dillmon, M. S., Frank, E. S., . . . Van Poznak, C. H. (2017). Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol, 35*(18), 2062-2081. doi:10.1200/jco.2016.70.7257

Donat, S., Diaz, M., Bishoff, J., Coleman, J., Dahm, P., Derweesh, I., . . . Chang, S. (2013). Follow-up for Clinically Localized Renal Neoplasms. *Clinical Guidelines.* Retrieved from http://www.auanet.org/guidelines/follow-up-for-clinically-localized-renal-neoplasms-(2013)

FDA. (2021). Devices@FDA. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm

Fuleihan, G. E.-H., & Brown, E. M. (2019, 8/28/2019). Parathyroid hormone secretion and action. *UpToDate.* Retrieved from https://www.uptodate.com/contents/parathyroid-hormone-secretion-and-action

Fuleihan, G. E.-H., & Juppner, H. (2020, 01/09/2020). Parathyroid hormone assays and their clinical use. *UpToDate.* Retrieved from https://www.uptodate.com/contents/parathyroid-hormone-assays-and-their-clinical-use

Fuleihan, G. E.-H., & Silverberg, S. J. (2020, 1/16/2020). Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation. *UpToDate.* Retrieved from https://www.uptodate.com/contents/primary-hyperparathyroidism-diagnosis-differential-diagnosis-and-evaluation

Gonzalez-Campoy, J. M., St Jeor, S. T., Castorino, K., Ebrahim, A., Hurley, D., Jovanovic, L., . . . Thomas, K. T. (2013). Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of

Endocrinology and the Obesity Society. *Endocr Pract, 19 Suppl 3*, 1-82. doi:10.4158/ep13155.Gl

Hamedanian, L., Badehnoosh, B., Razavi-Khorasani, N., Mohammadpour, Z., & Mozaffari-Khosravi, H. (2019). Evaluation of vitamin D status, parathyroid hormone, and calcium among Iranian pregnant women with preeclampsia: A case-control study. *Int J Reprod Biomed (Yazd), 17*(11), 831-840. doi:10.18502/ijrm.v17i10.5494

Han, C. H., Fry, C. H., Sharma, P., & Han, T. S. (2019). A clinical perspective of parathyroid hormone related hypercalcaemia. *Rev Endocr Metab Disord*. doi:10.1007/s11154-019-09529-5

Hanon, E. A., Sturgeon, C. M., & Lamb, E. J. (2013). Sampling and storage conditions influencing the measurement of parathyroid hormone in blood samples: a systematic review. *Clin Chem Lab Med, 51*(10), 1925-1941. doi:10.1515/cclm-2013-0315

Hernandez-Becerra, E., Jimenez-Mendoza, D., Mutis-Gonzalez, N., Pineda-Gomez, P., Rojas-Molina, I., & Rodriguez-Garcia, M. E. (2020). Calcium Deficiency in Diet Decreases the Magnesium Content in Bone and Affects Femur Physicochemical Properties in Growing Rats. *Biol Trace Elem Res*. doi:10.1007/s12011-019-01989-9

Hogan, J., & Goldfarb, S. (2019, 12/11/2019

). Regulation of calcium and phosphate balance. *UpToDate.* Retrieved from https://www.uptodate.com/contents/regulation-of-calcium-and-phosphate-balance

Jellinger, P. S., Handelsman, Y., Rosenblit, P. D., Bloomgarden, Z. T., Fonseca, V. A., Garber, A. J., . . . Davidson, M. (2017). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocrine Practice, 23*. Retrieved from https://pro.aace.com/pdfs/education/lipid-guidelines.pdf

KDIGO. (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int, 3*(1), v - 150. Retrieved from https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

KDIGO. (2017). KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). *Kidney Int, 7*(1), 1-59. Retrieved from https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf

Ketteler, M., Block, G. A., Evenepoel, P., Fukagawa, M., Herzog, C. A., McCann, L., . . . Leonard, M. B. (2017). Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int, 92*(1), 26-36. doi:10.1016/j.kint.2017.04.006

Konishi, H., Fujiwara, H., Itoh, H., Shiozaki, A., Arita, T., Kosuga, T., . . . Otsuji, E. (2018). Influence of magnesium and parathyroid hormone on cisplatin-induced nephrotoxicity in esophageal squamous cell carcinoma. *Oncol Lett, 15*(1), 658-664. doi:10.3892/ol.2017.7345

Kreepala, C., Kitporntheranunt, M., Sangwipasnapaporn, W., Rungsrithananon, W., & Wattanavaekin, K. (2018). Assessment of preeclampsia risk by use of serum ionized magnesium-based equation. *Ren Fail, 40*(1), 99-106. doi:10.1080/0886022x.2017.1422518

Leder, B. Z. (2017). Parathyroid Hormone and Parathyroid Hormone-Related Protein Analogs in Osteoporosis Therapy. *Curr Osteoporos Rep, 15*(2), 110-119. doi:10.1007/s11914-017-0353-4

Lederer, E. (2014). Regulation of serum phosphate. *J Physiol, 592*(18), 3985-3995. doi:10.1113/jphysiol.2014.273979

Magee, L. A., Pels, A., Helewa, M., Rey, E., & von Dadelszen, P. (2014). Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. *J Obstet Gynaecol Can, 36*(5), 416-441.

Mantovani, G., Bastepe, M., Monk, D., de Sanctis, L., Thiele, S., Usardi, A., . . . Linglart, A. (2018). Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. *Nat Rev Endocrinol*. doi:10.1038/s41574-018-0042-0

Mantovani, G., Bastepe, M., Monk, D., de Sanctis, L., Thiele, S., Ahmed, S. F., . . . Linglart, A. (2020). Recommendations for Diagnosis and Treatment of Pseudohypoparathyroidism and Related Disorders: An Updated Practical Tool for Physicians and Patients. *Hormone Research in Paediatrics, 93*(3), 182-196. doi:10.1159/000508985

Marcucci, G., Della Pepa, G., & Brandi, M. L. (2017). Drug safety evaluation of parathyroid hormone for hypocalcemia in patients with hypoparathyroidism. *Expert Opin Drug Saf, 16*(5), 617-625. doi:10.1080/14740338.2017.1311322

Mayo. (2018a). Calcium, 24 Hour, Urine. Retrieved from https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/36891

Mayo. (2018b, 2018). Magnesium, Serum. Retrieved from https://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8448

Mechanick, J. I., Apovian, C., Brethauer, S., Garvey, W. T., Joffe, A. M., Kim, J., . . . Still, C. D. (2019). CLINICAL PRACTICE GUIDELINES FOR THE PERIOPERATIVE NUTRITION, METABOLIC, AND NONSURGICAL SUPPORT OF PATIENTS UNDERGOING BARIATRIC PROCEDURES - 2019 UPDATE: COSPONSORED BY AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY, THE OBESITY SOCIETY, AMERICAN SOCIETY FOR METABOLIC & BARIATRIC SURGERY, OBESITY MEDICINE ASSOCIATION, AND AMERICAN SOCIETY OF ANESTHESIOLOGISTS - EXECUTIVE SUMMARY. *Endocr Pract, 25*(12), 1346-1359. doi:10.4158/gl-2019-0406

Mechanick, J. I., Youdim, A., Jones, D. B., Garvey, W. T., Hurley, D. L., McMahon, M. M., . . . Brethauer, S. (2013). Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocr Pract, 19*(2), 337-372. doi:10.4158/ep12437.Gl

NBA. (2015). Patient blood management guidelines: module 5 - obstetrics and maternity. Retrieved from https://www.guideline.gov/summaries/summary/49831/patient-blood-management-guidelines-module-5--obstetrics-and-maternity?q=calcium

NCCMH. (2014). National Institute for Health and Care Excellence: Clinical Guidelines. In *Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care*. Leicester (UK): British Psychological Society

(c) The British Psychological Society & The Royal College of Psychiatrists, 2014.
NCCN. (2018a). NCCN Clinical Practice Guidelines in Oncology Bone Cancer. *NCCN Guidelines, 2.2018*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
NCCN. (2018b). NCCN Clinical Practice Guidelines in Oncology Breast Cancer. *NCCN Guidelines, 1.2018*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
NCCN. (2018c). NCCN Clinical Practice Guidelines in Oncology Prostate Cancer. *NCCN Guidelines, 3.2018*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
NCCN. (2019). Bone Cancer - Version 1.2020 - August 12, 2019. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
NCCN. (2020a). Acute Lymphoblastic Leukemia Version 2.2021 - December 3, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
NCCN. (2020b). Bone Cancer - Version 1.2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
NCCN. (2020c). Esophageal and Esphagogastric Junction Cancers - Version 5.2020 - December 23, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
NCCN. (2020d). Kidney Cancer - Version 1.2021 - July 15, 2020

Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
NCCN. (2020e). Multiple Myeloma Version 4.2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
NCCN. (2020f). Multiple Myeloma Version 4.2021 - December 20, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
NCCN. (2020g). NCCN Clinical Practice Guidelines in Oncology: Bone Cancer. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
NCCN. (2020h). Neuroendocrine and Adrenal Tumors Version 2.2020 - July 24, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
NCCN. (2020i). Occult Primary (Cancer of Unknown Primary [CUP]) - Version 1.2021 Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf
NCCN. (2020j). Prostate Cancer - Version 3.2020 - November 17, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
NCCN. (2020k). Systemic Light Chain Amyloidosis - Version 1.2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf
NCCN. (2020l). T-Cell Lymphomas Version 1.2021 - October 5, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf
NCCN. (2020m). Thyroid Carcinoma - Version 2.2020 - July 15, 2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
NCCN. (2021a). Breast Cancer - Version 1.2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
NCCN. (2021b). Prostate Cancer - Version 1.2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

NGC. (2013). Heart failure in adults. Retrieved from https://www.guideline.gov/summaries/summary/47030/heart-failure-in-adults?q=magnesium

NICE. (2013). National Institute for Health and Clinical Excellence: Guidance. In *Hyperphosphataemia in Chronic Kidney Disease: Management of Hyperphosphataemia in Patients with Stage 4 or 5 Chronic Kidney Disease*. Manchester: National Institute for Health and Clinical Excellence (UK)

NICE. (2014a). Multiple sclerosis in adults: management. In.

NICE. (2014b). National Institute for Health and Care Excellence: Clinical Guidelines. In *Chronic Kidney Disease (Partial Update): Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care*. London: National Institute for Health and Care Excellence (UK)

NICE. (2014c). National Institute for Health and Care Excellence: Clinical Guidelines. In *Multiple Sclerosis: Management of Multiple Sclerosis in Primary and Secondary Care*. London: National Institute for Health and Care Excellence (UK)

NICE. (2015). National Institute for Health and Care Excellence: Clinical Guidelines. In *Suspected Cancer: Recognition and Referral*. London: National Institute for Health and Care Excellence (UK)

Orloff, L. A., Wiseman, S. M., Bernet, V. J., Fahey, T. J., 3rd, Shaha, A. R., Shindo, M. L., . . . Wang, M. B. (2018). American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults. *Thyroid, 28*(7), 830-841. doi:10.1089/thy.2017.0309

Pak, C. Y. C., Kaplan, R., Bone, H., Townsend, J., & Waters, O. (1975). A Simple Test for the Diagnosis of Absorptive, Resorptive and Renal Hypercalciurias. *New England Journal of Medicine, 292*(10), 497-500. doi:10.1056/NEJM197503062921002

Pearle, Goldfarb, D., Assimos, D., Gary Curhan, G., Denu-Ciocca, C., Brian R. Matlaga, B., . . . White, J. R. (2019). Medical Management of Kidney Stones (2019). Retrieved from https://www.auanet.org/guidelines/kidney-stones-medical-mangement-guideline

Pearle, M., Goldfarb, D., Assimos, D., Curhan, G., Denu-Ciocca, C., Matlaga, B., . . . White, J. (2014). Medical Management of Kidney Stones. *Clinical Guidelines.* Retrieved from https://www.auanet.org/guidelines/medical-management-of-kidney-stones-(2014)

Press, D. M., Siperstein, A. E., Berber, E., Shin, J. J., Metzger, R., Monteiro, R., . . . Mitchell, J. C. (2013). The prevalence of undiagnosed and unrecognized primary hyperparathyroidism: a population-based analysis from the electronic medical record. *Surgery, 154*(6), 1232-1237; discussion 1237-1238.

Quamme, G. A. (1986). Renal handling of magnesium: drug and hormone interactions. *Magnesium, 5*(5-6), 248-272.

Rodriguez-Ortiz, M. E., Canalejo, A., Herencia, C., Martinez-Moreno, J. M., Peralta-Ramirez, A., Perez-Martinez, P., . . . Almaden, Y. (2014). Magnesium modulates parathyroid hormone secretion and upregulates parathyroid receptor expression at moderately low calcium concentration. *Nephrol Dial Transplant, 29*(2), 282-289. doi:10.1093/ndt/gft400

Rooney, M. R., Alonso, A., Folsom, A. R., Michos, E. D., Rebholz, C. M., Misialek, J. R., . . . Lutsey, P. L. (2020). Serum magnesium and the incidence of coronary artery disease over a median 27 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study and a meta-analysis. *Am J Clin Nutr, 111*(1), 52-60. doi:10.1093/ajcn/nqz256

Ross, D. S., Burch, H. B., Cooper, D. S., Greenlee, M. C., Laurberg, P., Maia, A. L., . . . Walter, M. A. (2016). 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid, 26*(10), 1343-1421. doi:10.1089/thy.2016.0229

Shaker, J. L., & Deftos, L. (2018). Calcium and Phosphate Homeostasis. In K. R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, K. Dungan, A. Grossman, J. M. Hershman, G. Kaltsas, C. Koch, P. Kopp, M. Korbonits, R. McLachlan, J. E. Morley, M. New, L. Perreault, J. Purnell, R. Rebar, F. Singer, D. L. Trence, A. Vinik, & D. P. Wilson (Eds.), *Endotext*. South Dartmouth (MA): MDText.com, Inc.

Sturgeon, C. M., Sprague, S., Almond, A., Cavalier, E., Fraser, W. D., Algeciras-Schimnich, A., . . . Vesper, H. W. (2017). Perspective and priorities for improvement of parathyroid hormone (PTH) measurement - A view from the IFCC Working Group for PTH. *Clin Chim Acta, 467*, 42-47. doi:10.1016/j.cca.2016.10.016

Tieder, J. S., Bonkowsky, J. L., Etzel, R. A., Franklin, W. H., Gremse, D. A., Herman, B., . . . Smith, M. B. (2016). Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants. *Pediatrics, 137*(5). doi:10.1542/peds.2016-0590

Valcour, A., Zierold, C., Blocki, F. A., Hawkins, D. M., Martin, K. J., Rao, S. D., & Bonelli, F. (2018). Trueness, precision and stability of the LIAISON 1-84 parathyroid hormone (PTH) third-generation assay: comparison to existing intact PTH assays. *Clin Chem Lab Med*. doi:10.1515/cclm-2018-0217

Wilhelm, S. M., Wang, T. S., Ruan, D. T., & et al. (2016). The american association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surgery, 151*(10), 959-968. doi:10.1001/jamasurg.2016.2310

Wojda, S. J., & Donahue, S. W. (2018). Parathyroid hormone for bone regeneration. *J Orthop Res, 36*(10), 2586-2594. doi:10.1002/jor.24075

Wright, M., Southcott, E., MacLaughlin, H., & Wineberg, S. (2019). Clinical practice guideline on undernutrition in chronic kidney disease. *BMC Nephrol, 20*(1), 370. doi:10.1186/s12882-019-1530-8

IX. Review/Revision History

Effective Date	Summary
05/15/2022	Initial Policy Implementation