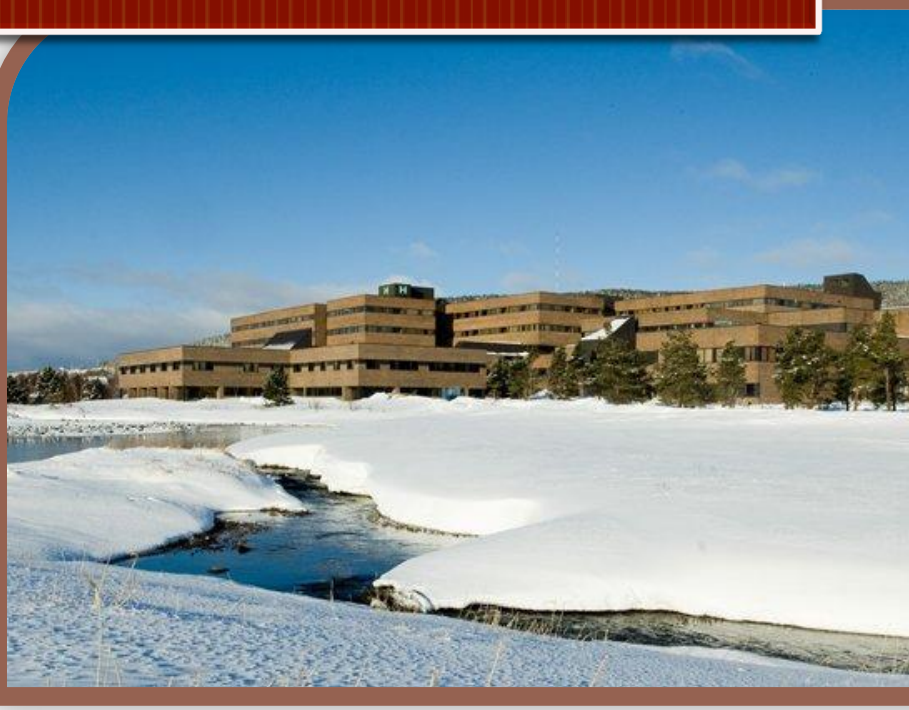
# Parathyroid Hormone and calcium status testing



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## Executive Summary

All health professionals with test ordering privileges can order intact Parathyroid hormone (PTH) tests. Use of this test must be restricted to patients at high risk of parathyroid dysfunction and/or based on unexplained abnormalities in calcium homeostasis. Hence, PTH test ordering will be available under the following conditions and consistent with the following guidelines:

*Images provided courtesy of HSIMS*

1. All cases of unexplained hypercalcemia and hypocalcemia **must** be confirmed by correction of total calcium for albumin, or by measurement of ionized calcium prior to investigations involving PTH testing.
2. Diagnostic testing algorithms for hypercalcemia and hypocalcemia should be used to guide diagnostic workup and to assist with interpretation of PTH levels.
3. PTH testing will be subject to a minimum reorder interval of 30 days for out-patients only.
4. PTH orders will **only** be completed if the indication for the order is provided with the original test request (either on the test requisition or accompanying Laboratory Test Special Authorization Form). Acceptable indications for PTH testing include:
   a. Test ordered **STAT** from **OR** or **by surgeon** (during or post -parathyroid & thyroid surgery)**.**
   b. Confirmed **hypercalcemia** or **hypocalcemia**.
   c. PTH monitoring in **CKD** patient.
   d. A completed authorization form indicating:
      i. **Monitoring Parathyroid disease** (e.g. monitoring disease progression, bisphosphonate therapy, or Parathyroid cancer).
      ii. **Test directed by an endocrinologist** (Identify the name of the specialist).
      iii. **High risk for parathyroid disease** (e.g. High risk for secondary hyperparathyroidism.)
5. PTH test orders not meeting any of the above criteria will be cancelled.

### Disclaimer

These recommendations have been developed by the Clinical Biochemistry Laboratory Formulary Working Group on behalf of the Laboratory Medicine Program of Eastern Health Authority. The recommendations are intended to provide guidance for appropriate usage of specific laboratory tests, and to outline preferred approaches to the investigation and management of clinical problems using the identified tests. The recommendations may not apply to all clinical scenarios and are not intended to substitute for the advice or professional judgment of a health care professional, nor are they intended to be the only approach to the management of specific clinical problems identified.

## Contents

## Scope

These recommendations apply to:

- Investigation of unexplained hypercalcemia and hypocalcemia.
- Investigation of patients at high risk for parathyroid disease and monitoring patients being treated for parathyroid disease, where measurement of PTH is being considered.

## Rationale

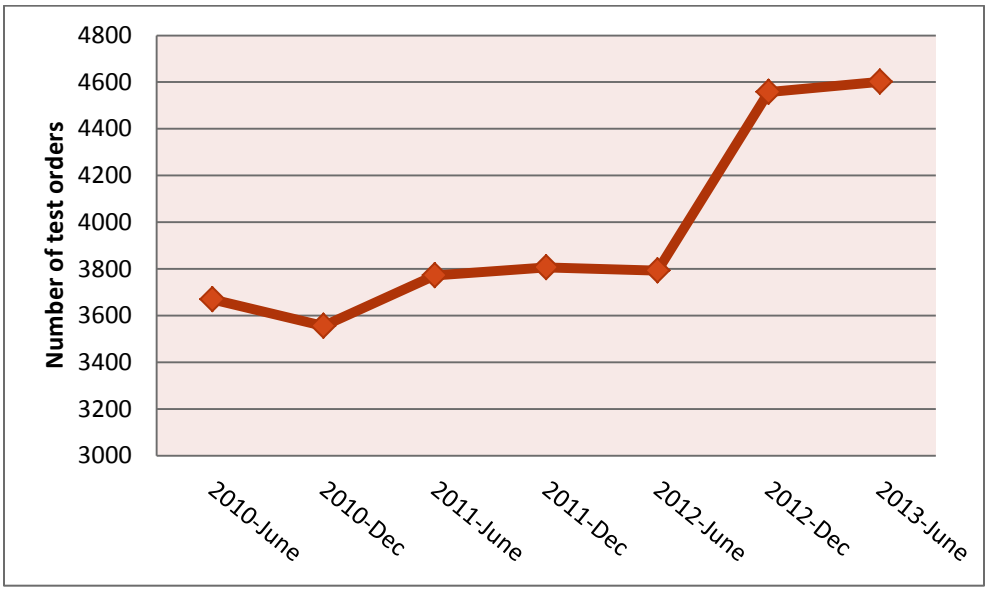
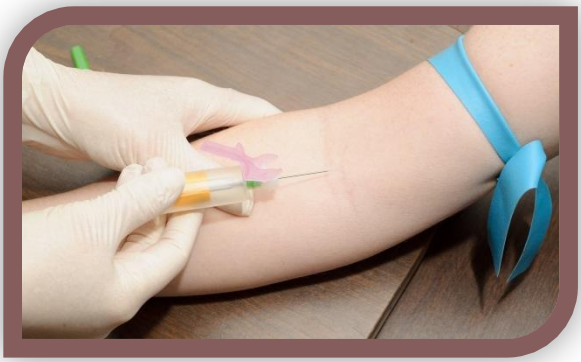



**Figure 1. Number of PTH tests ordered from 2010 to 2013 and performed in Eastern Health Laboratories.**

There has been a modest climb in the number of laboratory requests for PTH over the past couple of years. This increase has coincided with an increase in unnecessary referrals especially in situations where PTH is elevated but serum calcium is normal. In many of these cases, PTH was done as part of an initial investigation of patients for vague or non-specific symptoms such as fatigue or malaise or during a routine check-up. Interpretation of PTH can be challenging as PTH levels are not only affected by calcium homeostasis, but also vitamin D status, and even different laboratory methodologies can have dramatic effects on the final measured levels.

In the majority of cases, the usefulness of PTH testing in general practice involves investigation of unexplained abnormalities in serum calcium levels. An algorithmic approach directing clinical decision making and laboratory workup is recommended whenever PTH testing is done to investigate calcium abnormalities.

## Background



The parathyroid glands represent 4 small glands located in the neck and immediately behind the thyroid gland. The main function of this gland is to help maintain calcium homeostasis by producing parathyroid hormone (PTH). The parathyroid gland responds to blood calcium levels under a strong negative-feedback loop by increasing synthesis and secretion of PTH when calcium levels fall (hypocalcemia) below the individual's homeostatic set-point for blood calcium. PTH release is also dependent on adequate magnesium, and very low blood magnesium can decrease blood PTH with consequent reduction in blood calcium levels. PTH increases phosphate excretion by the kidney; increases mobilization of calcium from bone; and stimulates conversion of 25-hydroxyvitamin D to 1, 25 dihydroxyvitamin D. This latter product increases absorption of dietary calcium from the small intestines. Hence, abnormalities in PTH production are often indicated by changes in blood calcium levels or by clinical symptoms of hyper or hypocalcemia.

## Assessment of Calcium homeostasis

About 50% of the measured total calcium level is in a physiologically inactive albumin-bound form. The physiologically active form of calcium is ionized calcium, but it can be difficult to measure as it requires special sample processing procedures and is done by relatively manual laboratory methods. An alternative approach for addressing whether abnormal calcium levels are physiologically relevant is to correct for albumin concentration prior to interpreting. Several different equations have been published to correct total calcium levels, all of which have shortcomings. **It is important that only equations with accuracy validated by the local clinical laboratory be used.** Minor discordances in classifying hyper- or hypocalcemia occur in up to 25% of cases classified by albumin correction compared with ionized calcium measurements. The main laboratory induced error for total calcium measurements occurs when the phlebotomist leaves the tourniquet in place for an excessively long period of time. The tourniquet effect is usually very modest and typically about 0.05 mmol/L. So consideration of this effect is mainly important when distinguishing normal calcium levels from mild hypercalcemia. It is unlikely that prolonged use of the tourniquet will cause a normocalcemic person to appear to have moderate hypercalcemia , or for someone with moderate hypercalcemia to be thought to have severe hypercalcemia. Use of the tourniquet can have a greater effect on ionized calcium because a decrease in blood pH causes calcium to dissociate from albumin, becoming free or ionized. In extreme situations artificially high calcium results can occur when there is gross hemolysis. Other discordances may occur in malignancy, and in the case of multiple myeloma or MGUS, where the monoclonal protein may bind to significant amounts of calcium leading to a high total calcium, but normal ionized calcium. For this reason, measurement of ionized calcium is advisable as a follow-up test for patients with high total calcium measurements and monoclonal proteins. Other causes of moderate to severe

hypercalcemia probably do not need ionized calcium done to confirm it. Ionized calcium measurements are most important for mild cases of hypercalcemia . Conversely, essentially ALL hypocalcemia should be confirmed by an ionized calcium level. Ionized calcium measurement is the preferred laboratory parameter to use when interpreting PTH results, when assessing patients for hyperparathyroidism, hypoparathyroidism, malignancy, MGUS, or renal disease.

## Investigation of hypercalcemia

The two main causes of hypercalcemia are primary hyperparathyroidism and malignancy. In an outpatient, primary hyperparathyroidism is somewhat more likely, while malignancy is the more likely cause in the inpatient. Together these explain >95% of confirmed hypercalcemia cases. Measurement of PTH levels is helpful in distinguishing the two main causes of hypercalcemia. PTH can be “inappropriately normal” (usually at the upper end of the reference range) or increased in primary hyperparathyroidism, but suppressed or undetectably low if malignancy is the cause of hypercalcemia. Most other causes of hypercalcemia will also lead to undetectable PTH. Exceptions to this are the comparatively rare cases of Familial Hypocalciuric Hypercalcemia (FHH), neonatal severe primary hyperparathyroidism, or in the case of parathyroid carcinoma. It is advisable to temporarily discontinue thiazide diuretics or lithium therapy when evaluating mild cases of hypercalcemia with suppressed PTH. Explanation of hypercalcemia depends on the levels of PTH. A finding of low PTH or low normal PTH (within the lower quartile of the normal range) suggests a non-PTH related cause for the hypercalcemia. However, finding a PTH level well within the normal range with confirmed hypercalcemia strongly suggests a PTH-mediated cause. **We recommend usage of Algorithm 1 when working up unexplained cases of hypercalcemia.**

Measurement of PTH is useful in the differential diagnosis of confirmed cases of hyper and hypocalcemia; for investigating suspected cases of hyperparathyroidism (primary, secondary, and tertiary) or hypoparathyroidism; and for monitoring osteodystropy in end-stage renal disease. Measurement of PTH during parathyroid surgery is the only accepted rationale for STAT PTH measurements.The incidence and prevalence of primary hyperparathyroidism is about 2 and 10 in 10,000, respectively, with a hyper-secreting parathyroid adenoma being the most common cause. The unabated secretion of PTH eventually leads to hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia. In primary hyperparathyroidism, the increase in serum calcium level is usually mild and stable, but can be slowly progressive over a period of years. Over the long term this can lead to dehydration, development of renal stones, hypertension, gastrointestinal disturbances, osteoporosis and sometimes neuropsychiatric and neuromuscular problems.

## Investigation of hypocalcemia

Thyroid surgery is the most common cause of hypoparathyroidism, but autoimmune etiology is also relatively common. Hypo-secretion of PTH due to magnesium deficiency or due to pseudohyperparathyroidism is rarely the cause of hypocalcemia.

Primary hypoparathyroidism is typically identified by low or "inappropriately normal" PTH in the setting of low blood calcium. The characteristic symptoms of primary hypoparathyroidism are

essentially those of hypocalcemia and include weakness, tetany, and possible optic nerve atrophy. Patients with renal impairment, kidney stones, Osteoporotic fractures, or Granulamatous diease (Sarcoidosis or tuberculosis) are considered at high risk for hypocalcemia, but can have inappropriately normal or high PTH. Nearly all renal failure patients have high PTH (1-84 intact peptide) with initial increases occurring early in the disease course while the serum phosphate is still normal, but increases as hyperphosphatemia and hypocalcemia progresses. Long-standing secondary hyperparathyroidism can lead to tertiary hyperparathyroidism as hypersecretion of PTH becomes autonomous. Secondary hyperparathyroidism can also be identified while investigating patients with eating disorders, malabsorptive disorders, recurrent kidney stones, or hyperphosphatemia. **We recommend usage of Algorithm 1 when working up unexplained cases of hypocalcemia.**

## Appropriate use of PTH testing for other conditions

In general, PTH should only be used to investigate cases of unexplained calcium abnormalities. Exceptions to this are patients considered at high risk for parathyroid disease. This includes cases of osteoporosis and bone loss to rule out secondary hyperparathyroidism. Also at high risk for secondary hyperparathyroidism are patients in renal failure, with hyperphosphatemia, eating disorders, recurrent kidney stones, and malabsorptive disorders. PTH monitoring may also be required with parathyroid gland imaging studies (nuclear medicine, PET, and ultrasound) and assist in decision making on the need for surgery. A finding of increasing PTH levels with negative initial scanning may suggest need for further imaging studies to identify a source. PTH can increase without a change in serum or ionized calcium if the excess calcium is excreted in the urine. PTH measurements are also useful when Cinacalcet is used to help resolve symptoms of hypercalcemia by suppressing PTH, in patients with primary hyperparathyroidism. Bisphosphonates are used to medically treat patients with primary hyperparathyroidism who initially postpone surgery. Bisphosphonates lower the serum calcium and protect the bones but not the kidneys. PTH levels are done in these situations to determine whether the primary hyperparathyroidism is progressing or not. While in general total calcium and ionized calcium is more appropriate for monitoring parathyroid disease, there are occasionally situations where PTH monitoring is needed.

Measurement of 24 hour urine calcium is generally of little diagnostic value. High urine calcium levels are not diagnostic for primary hyperparathyroidism, and do not reliably discriminate primary hyperparathyroidism from FHH. This urine test should not be used for routine assessment of calcium homeostasis. Its potential utility remains as a decision tool when evaluating primary hyperparathyroid cases for possible surgery. Very high urine calcium excretion indicates a high risk for nephrocalcinosis (and eventual renal insufficiency) and nephrolithiasis (kidney stones).

## Conclusions

Investigations for abnormalities in calcium homeostasis should begin with measurement of total calcium (Algorithms 1 & 2). Follow-up testing should include confirmation of the abnormality and use of other investigations including iPTH to arrive at a diagnosis. Appropriate use of tests for assessment of calcium homeostasis is summarized in Table 1.

**Table 1. Recommended Usage of Tests.**

| | |
|---|---|
| Total Calcium | •Front line test for assessment of calcium homeostasis in non-complex cases . |
| Ionized Calcium | •To confirm all cases of hypocalcemia.<br>•To confirm mild elevations in calcium (<0.1 mmol/L above the upper limit of normal). |
| Albumin-Corrected Calcium | •To confirm mild to severe hypercalcemia (>0.1 mmol/L above the upper limit of normal). |
| PTH | •To investigate unexplained calcium abnormalities.<br>•To investigated high risk cases for parathyroid disease.<br>•To monitor parathyroid disease. |
| 24h Urinary Calcium | •For specialist use to distinguish FHH from primary hyperparathyroidism.<br>•To assist in managment decisions for nephrocalcinosis or nephrolithiosis. |

## Clinical Biochemistry Laboratory Formulary Committee

The Clinical Biochemistry Laboratory Formulary Committee is a multidisciplinary group involved in improving the usage of laboratory services within Eastern Health.

The main purposes of the committee include:

1. Assisting in decision making on in-house testing menus including retiring of redundant tests and adding of new tests.
2. Reviewing and advising on issues related to laboratory utilization to promote evidence-based usage of laboratory services and best practices guidelines.
3. Advising on development of a tiered formulary for all laboratory tests available through the Clinical Biochemistry laboratory.

We acknowledge the following as committee members in development of this guideline:

- Dr. Brendan Barrett
- Dr. Paul Bonisteel
- Barry Dyer
- Dr. Christopher Kovacs
- Natasha Lee
- Peggy Manning
- Colleen Mercer
- Dr. David Parry
- Dr. Edward Randell
- Dr. Robert Woodland

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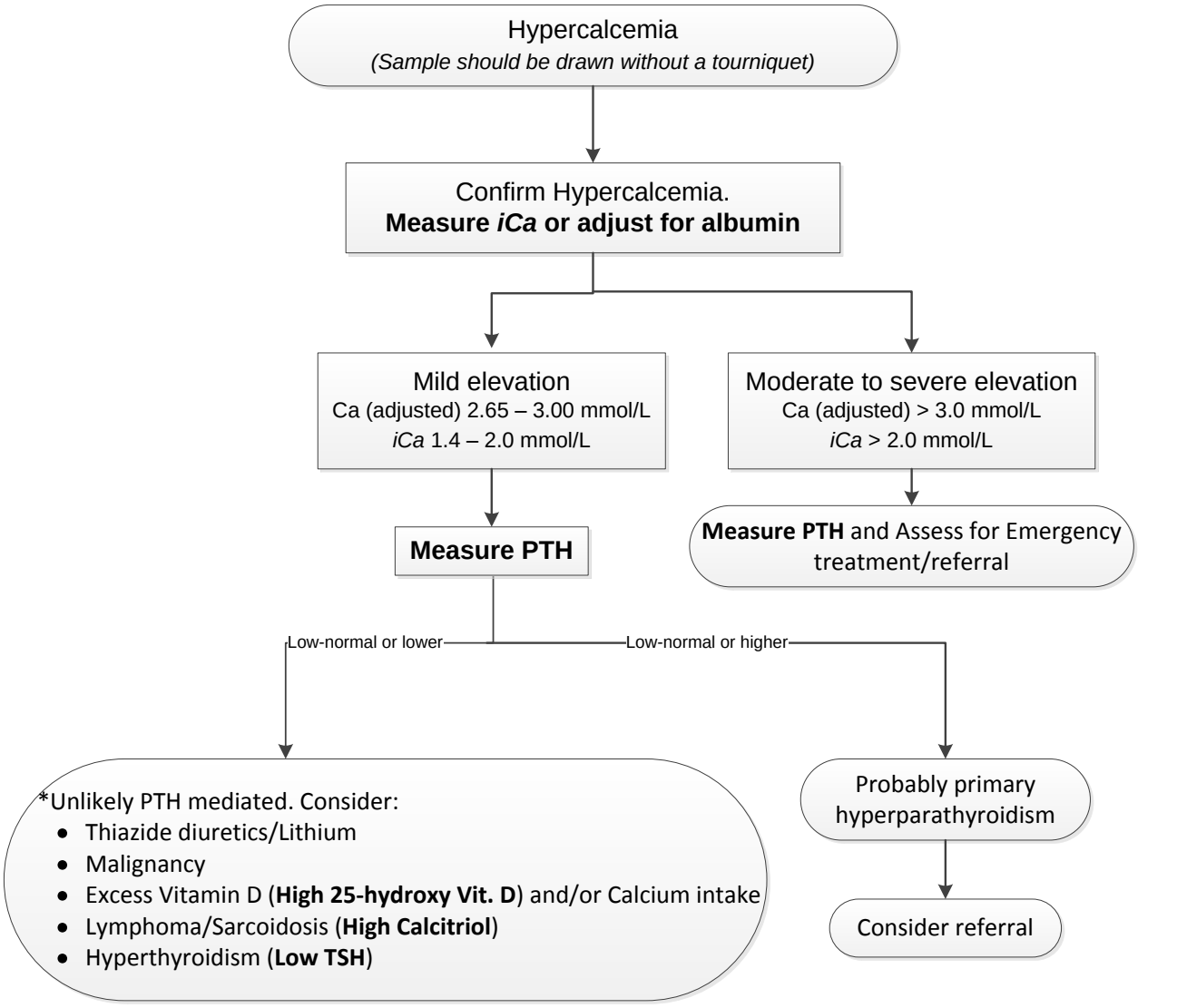
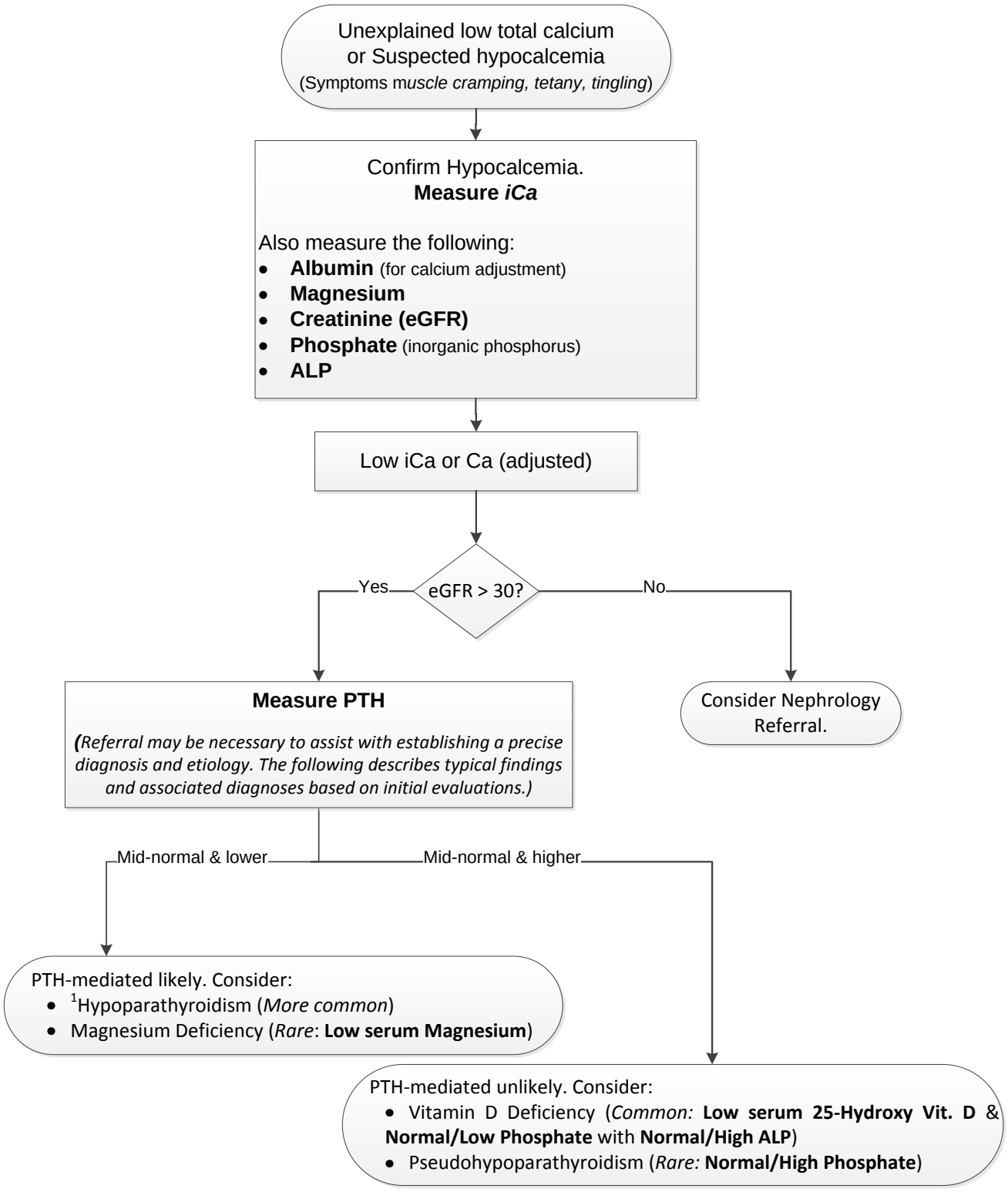
## Appendix 1




*** Please Note:**

- Low levels of PTH below the lower reference limit is consistent with non-PTH medicated causes of hypercalcemia.
- PTH levels in the lower 1/3 for the reference range may be considered equivocal and require referral to a specialist to help resolve the cause of hypercalcemia.
- PTH levels above the lower 1/3 of the reference range are consistent with PTH-mediated hypercalcemia.

## Appendix 2




[1]**Please Note**: Mid to low normal PTH occasionally occurs in hypoparathyoidism when inactive but detectable forms of PTH are present. These cases should be considered as ”inappropriately normal PTH”.