A raised calcium result should prompt a request for a repeat on an un-cuffed sample and any medications that elevate calcium should be reviewed (thiazides, lithium, Vitamin D or A). If calcium is persistently raised parathyroid hormone (PTH) should be checked.
However, if calcium >3.4 mmol/l or the patient is symptomatic outpatient investigation is not appropriate and the patient should be admitted.
This guideline refers to the outpatient management of hypercalcaemia with a raised PTH.

**Primary Hyperparathyroidism**

Primary hyperparathyroidism is a disorder of the parathyroid glands in which one or more of the parathyroid glands are enlarged (hyperplastic), overactive, and secrete too much parathyroid hormone, which results in hypercalcaemia. Clinical features may include bone resorption and osteoporosis, calcium deposits in the kidneys, muscular weakness, nausea, vomiting, abdominal pains, and drowsiness.

Hyperparathyroidism is also associated with Multiple Endocrine Neoplasia types 1 and 2a.

Primary hyperparathyroidism is defined as persistent hypercalcaemia with an inappropriately elevated or normal PTH. There is usually hypercalciuria. Elevated calcium would usually suppress PTH through negative feedback. Therefore low or unmeasurable values indicate a non-parathyroid cause, of which malignancy is the most common. Of course malignancy and hyperparathyroidism can co-exist causing diagnostic confusion.

**Familial Benign Hypercalcaemia**

(Also known as familial hypocalciuric hypercalcaemia)

This condition is caused by a loss of function mutation in the calcium sensing receptor (CaSR) that is inherited as an autosomal dominant trait. This causes continued PTH release despite hypercalcaemia, and therefore can present similarly to primary hyperparathyroidism. However, the difference is that there is reduced calcium excretion in the urine.

It is generally a benign, asymptomatic condition although pancreatitis, gall stones and chondrocalcinosis have been reported. Parathyroidectomy has no benefit and therefore it is important to exclude prior to considering surgery.

Prevalence of FBH is unknown but has been quoted as 1/78000. However, in those patients with hypercalcaemia the prevalence could be as high as 1/200, if the PTH is raised this becomes 1/20. However, if PTH is between 2.6 and 6.9 pmol/l the prevalence is 1/4.
Diagnosis and Management of Primary Hyperparathyroidism in Primary Care

• In general, patients with calcium >3.4 mmol/l or who are significantly symptomatic should be admitted for urgent treatment and assessment.

• An urgent referral to endocrinology via fax 0117 414 8129 can be arranged if calcium is >3.0mmol/l or if there are symptoms.

• High calcium, Low PTH is consistent with non-parathyroid hypercalcaemia
There is ambiguity around the PTH lower cut off and as to when primary hyperparathyroidism is ruled out. The third international workshop on the diagnosis of asymptomatic primary hyperparathyroidism (JCEM 2009) suggests that PTH is usually in the upper half of the reference range or elevated with primary hyperparathyroidism. However, PTH levels as low as 2.6pmol/l have been noted therefore most clinicians use this as a threshold below which alternative causes for hypercalcaemia must be sought.
The most common cause of hypercalcaemia with a suppressed PTH is malignancy. Other causes include vitamin D excess, sarcoidosis, endocrinopathy (including Thyrotoxicosis, Phaeochromocytoma, Addison’s, and Acromegaly).

• High calcium, Normal/Elevated PTH would most likely indicate Primary Hyperparathyroidism
The following steps are required to determine the severity of disease and to determine management;

1. Exclude Vitamin D Deficiency
Vitamin D inadequacy should be ruled out in all patients with primary hyperparathyroidism. It increases the severity of the disease, can mask hypercalcaemia, increases the risk of parathyroid tumorigenesis and leads to higher post-operative risk (hungry bone syndrome and persistently elevated PTH).
   » If vitamin D is less than 50umol/l it should be treated.
   » During vitamin D replacement careful monitoring is required and repeat calcium is recommended after 2 weeks.
   » PTH and calcium should be repeated 3 months after vitamin D treatment.

2. Assess the need for referral.
In asymptomatic individuals with calcium < 3.0 mmol/l, the decision as to whether they require a referral depends on the risk of complications. Chronically elevated PTH causes osteoporosis, renal impairment and renal calculi. Therefore, routine referral is indicated if the patient meets any of the following criteria;
   • <70 years of age
   • Calcium > 2.79 mmol/L
   • eGFR 30-44ml/min/1.73m2
   • Symptomatic (including renal stones)
   • History of osteoporosis or fracture

3. Community management.
Patients who are asymptomatic and do not meet the referral criteria may be managed in primary care as follows;

a) Once vitamin D deficiency has been excluded a diagnosis of Primary hyperparathyroidism can be made.
b) Calcium and PTH should be checked again in 3 months but if they still do not fulfil referral criteria annual monitoring of calcium, PTH and renal function is advised.
c) Those who have required vitamin D replacement should be reassessed at 3 months to assess if they now meet referral criteria.
d) A 2 site DEXA scan should be considered every 2-3 years to assess for osteoporosis.
e) If they become symptomatic or meet the criteria for referral then this should be arranged.

**Calcium excretion ratio**

- Fast overnight, collect the second voided urine in a universal container.
- Send urine for calcium and creatinine
- This needs pairing with a fasted serum calcium and creatinine.

Calcium Excretion (µmol/L glomerular filtrate) assumes the patient is hypercalcaemic and is calculated according to the following formula:

\[
CaE = \frac{\text{urine Ca (mmol/L) x serum creatinine (µmol/L)}}{\text{urine creatinine (mmol/L)}}
\]

**Interpretation of Calcium excretion ratio (CaE)**

If hypercalcaemic patients have a CaE of less than 22 µmol/L glomerular filtrate they should be considered possible cases of FBH.

The best biochemical discrimination between patients with FBH and primary hyperparathyroidism is obtained by a fasted calcium excretion index (CaE) according to Gunn et al. At this cut off the sensitivity and specificity of the test is 95 and 92% respectively.

Definitive diagnosis requires family studies and the demonstration of hypercalcaemia in at least one first degree relative, a pattern of inheritance consistent with autosomal dominant transition and absence of signs of multiple endocrine neoplasia within the family. Gunn et al also suggested a definitive diagnosis could be reached by plotting CaE against PTH but now that genetic testing is available it has clarified the diagnostic pathway.
Appendix 1

Alternative methods for differentiation of FBH and Primary hyperparathyroidism;

• 24 hour urine calcium/creatinine clearance ratio = \( \frac{(\text{Urine calcium} \times \text{serum creatinine})}{(\text{Serum calcium} \times \text{urine creatinine})} \)

The American association of clinical endocrinologist and American association of endocrine surgeons position statement on diagnosis and management of primary hyperparathyroidism still suggests a 24hr Ca/Cr ratio using the following cut offs;
Possible FBH = Ca/Cr < 0.01
Primary Hyperparathyroidism = Ca/Cr >0.02
Sensitivity 85% and specificity 88%

It has not been validated for use on a spot urine calcium/creatinine ratio although it is often used in this way.

Appendix 2

**PTH/Calcium coded comments**
To be added at DCB discretion and with consideration of the degree of hypercalcaemia and degree of PTH elevation.

**Hypercalcaemia with no previous history, PTH etc.**
HCAL Raised calcium. If cause not known suggest repeat to confirm with a separate EDTA sample for PTH.
Suggest also review medications (e.g. thiazide diuretics may worsen hypercalcaemia).

**Significant hypercalcaemia (>3.00 + PTH >1.6)**
HCAL1 Significantly raised calcium. Urgent endocrinology referral is recommended (by FAX: 0117 414 8129).

**In hypercalcaemia**

- PTH > ~2.6 and if any of the following:
  - < 70 years of age
  - Calcium > 2.79 mmol/L
  - eGFR 30-44 (CKD 3b)
  - Symptomatic (including renal stones)
  - History of osteoporosis or fracture

HPTHR Probable primary hyperparathyroidism.
Check vitamin D status, replace if deficient and re-check calcium after 2 weeks. When vitamin D replete, send paired fasting serum calcium and
creatinine with an early morning urine (second void) samples for calcium and creatinine. A routine referral to endocrinology is indicated.

**PTH > ~2.6 and if patient does not meet criteria for referral listed above:**

**HPTh1**
Probable primary hyperparathyroidism.
Check vitamin D status, replace if deficient and re-check calcium after 2 weeks.
Refer to endocrinology if symptomatic, if there is a history of osteoporosis or fracture or if adjusted calcium rises to > 2.79 mmol/L. If patient is asymptomatic calcium should be checked after 3 months and monitored annually if stable. There is no need to recheck PTH. For further information please refer to the clinical guideline “Hypercalcaemia in Primary Care” available on the Severn Pathology website: http://www.nbt.nhs.uk/severn-pathology.

**PTH 1.6 - ~2.6**
Possible primary hyperparathyroidism, although other causes of hypercalcaemia/co-existing pathology should also be considered.
Check vitamin D status, replace if deficient and re-check calcium after 2 weeks.
Refer to endocrinology if symptomatic or if there is a history of osteoporosis or fracture.
For further information please refer to the clinical guideline “Hypercalcaemia in Primary Care” available on the Severn Pathology website: http://www.nbt.nhs.uk/severn-pathology.

**PTH <1.6**
LPTH
PTH not indicative of primary hyperparathyroidism.
Suggest symptom led investigations for other causes of hypercalcaemia.

**PTH >6.9 in normocalcaemia:**

**PTHNC**
Raised PTH in normocalcaemia is usually consistent with vitamin D deficiency.

**PTH <6.9 in hypo-calcaemia:**

**PTHLC**
PTH inappropriately low in hypocalcaemia, consistent with hypoparathyroidism. Causes include magnesium deficiency, autoimmune disease or acquired e.g. previous neck surgery.

**PTH 1.6-6.9 in normocalcaemia:**

**NCAL**
PTH appropriately within the reference range in normocalcaemia. These results do not suggest any abnormality in calcium metabolism.
CaE index >22 umol/L glomerular filtrate:

HCAE  Probable primary hyperparathyroidism. Familial hypercalcaemic hypocalciuria excluded.

CaE index <22 umol/L glomerular filtrate:

LCAE  Possible benign familial hypercalcaemic hypocalciuria.

References

2. Diagnosis of asymptomatic primary hyperparathyroidism; Proceedings of third international workshop. J Clin Endocrinol metab. 2/2009; 94(2); 340-350
4. The American association of clinical endocrinologists and the American association of endocrine surgeons position statement on the diagnosis and management of primary hyperparathyroidism. Endocrine Practice vol11 No1 Jan 2005;49