National Institute for Health and Care Excellence

Draft for consultation

Hyperparathyroidism (primary): diagnosis, assessment and initial management

[B] Evidence review for Diagnostic Tests

NICE guideline

Diagnostic evidence review

November 2018

Draft for consultation

This evidence review was developed by the National Guideline Centre

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1.1 Review question

1.1.1 Which biochemical test or combination of tests should be used for diagnosing primary hyperparathyroidism (for example, levels of parathyroid hormone, blood calcium and phosphate, alone or in combination)?

1.2 Introduction

Primary hyperparathyroidism (PHPT) is a biochemical diagnosis and is usually made by finding a raised or inappropriately normal serum PTH concentration in the presence of hypercalcemia. In addition, it is now recognised that some people have high-normal serum calcium levels with elevated parathyroid hormone called normocalcaemic PHPT. There are some rare but important differential diagnoses to be bear in mind when considering PHPT, for example familial hypocalciuric hypercalcemia (FHH).

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years and over) with suspected primary hyperparathyroidism due to one of the following: 1. Presenting with hypercalcaemia (adjusted serum calcium above 2.6mmol/L) with or without symptoms. 2. Presenting with an adjusted serum calcium level within the reference range (2.2-2.6mmol/L) but would be suspected to have PHPT due to end-organ damage or an incidental raised PTH level. These people would have suspected normocalcaemic PHPT. Population strata: • Presenting with hypercalcaemia versus normocalcaemia • Pregnant women with suspected PHPT Exclusions: • Patients under 18 years old • General population screening (patients not suspected to have PHPT due to one of the above reasons) • Established diagnosis of PHPT
Target condition	Suspected primary hyperparathyroidism
Index tests	• Assess the accuracy of morning PTH, fasting PTH and random PTH • Find the optimal threshold for the diagnosis of PHPT (trade- off between over and under referral to secondary care). • The above will be in a primary care setting. ○ Ionised calcium ○ Phosphate (morning versus fasting versus random test) ○ Urinary calcium excretion (24 hour urine calcium versus spot urine calcium) ○ Alkaline phosphatase ○ Vitamin D ○ Calcium/creatinine clearance ratio (CCCR) (calculated from simultaneous determinations of plasma levels and 24-h renal excretions of calcium and

	creatinine) ○ Calcium/creatinine excretion ratio (calculated from simultaneous determinations of serum and urine levels of calcium and creatinine) ○ 24 hour (urine) calcium/creatinine excretion ratio, mmol/mmol ○ 24 hour (renal) calcium excretion, mmol per 24 hours ○ Bone turnover markers
Reference standard	PHPT diagnosed by histology following parathyroidectomy (histology includes a descriptive characterisation of cell type and conclusion of parathyroid adenoma).
Outcomes	Outcomes for test and treat review: • Mortality • Quality of life • Number of people receiving treatment, i.e., including people who may not have needed it such as those with false positive results) • Repeat testing / additional testing • Timing of the test • Adverse events related to test (as reported in the papers) • Adverse events related to treatment (as reported in the papers) • preservation of end organ function (bone mineral density, fractures, renal stones and renal function) • persistent hypercalcaemia • cardiovascular events • cancer incidence Outcomes for diagnostic accuracy review: • Specificity • Sensitivity • Positive and / or negative predictive value • ROC curve or area under curve
Study design	• RCTs (for test-and-treat) • Cross-sectional studies / cohort studies / single-gate studies (for diagnostic accuracy) Exclusions: Two-gate case control studies (for example, a study recruiting one group of people in whom a diagnosis has already been established and another group of healthy controls), case-series

1.4 Clinical evidence

1.4.1 Included studies

This review aimed to assess the biochemical tests or combination of tests that should be used for diagnosing primary hyperparathyroidism. One study, Christensen 2008[13] was included in the review. The study evaluated the discriminative power of calcium creatinine excretion ratio, 24-hour renal calcium/creatinine clearance ratio and 24-hour renal calcium excretion for the separation between FHH and PHPT.

No relevant diagnostic test accuracy studies of index tests: PTH, ionised calcium, phosphate (morning versus fasting versus random test), and alkaline phosphatase in people under investigation for suspected primary hyperparathyroidism were identified.

The included study is summarised in Table 2 below.

1.4.2 Excluded studies

See the excluded studies list in appendix H.

Table 2: Summary of clinical studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Christensen 2008[13] Denmark	n=54 hypercalcaemic (17 males and 37 females, aged 18-75 years) with familiar hypocalciuric hypercalcaemia (FHH) a clinically significant mutation in the CASR gene and no clinical signs of parathyroid adenoma. n=97 patients with PHPT (17 males and 80 females aged 19-86 years). All PHPT patients were hypercalcaemic with elevated or high normal plasma PTH.	PHPT FHH	24 h renal calcium excretion (mmol, measured directly in the urine) 24 h renal calcium/creatinine excretion ratio (mmol/mmol) calcium/creatinine clearance ratio	Reference standard for PHPT- Histopathological findings at neck exploration leading to normocalcaemia in all PHPT cases. The reference standard for FHH- genetic studies confirming a clinically significant mutation in all FHH patients.	Patients on lithium treatment, which may stimulate FHH biochemically and eventually elicit PHPT, were excluded from the study.

Table 3: Clinical evidence summary: Receiver operating characteristic (ROC) curve analysis for discrimination between patients with familiar hypocalciuric hypercalcaemia (FHH) and patients with PHPT [modified GRADE table]

Index Test (Threshold)	Number of studies	N	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (SE)
24 h renal calcium excretion (CE) (mmol, measured directly in the urine) Cut-off point <5.45[b]	1	n = 54 FHH; n=97 PHPT	VERY LOW[a,d] due to risk of bias and indirectness	87	72.2	0.867 (0.029)
24 h renal calcium/creatinine excretion ratio (CR) (mmol/mmol) Cut-off point <0.52 [c]	1	n = 54 FHH; n=97 PHPT	VERY LOW[a,d] due to risk of bias and indirectness	88.9	81.4	0.903 (0.027)
calcium/creatinine clearance ratio (CCCR)[c] Cut-off point <0.0115 [b]	1	n = 54 FHH; n=97 PHPT	VERY LOW[a,d] due to risk of bias and indirectness	79.6	87.6	0.923 (0.021)

The committee deemed the sensitivity and specificity as equally important for decision-making.

[a] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[b] Cut-off points are for the diagnosis of FHH

[c] Overlap performance analysis disclosed that the CCCR included fewer patients with PHPT together with the FHH patients than the other two variables at different cut-off points.

[d] Population was with a confirmed diagnosis of PHPT

Narrative evidence:

Post-hoc overlap analyses (Christensen 2008):

Overlap performance analysis disclosed that the CCCR included fewer patients with PHPT together with the FHH patients than the other two variables at different cut-off points. The overlap performance analyses for the three variables of renal calcium handling using fixed FHH sample sizes showed that -to sample 100% of all patients with FHH (diagnostic sensitivity = 1), a cut-off point of < 0·027 should be used for CCCR, < 1·84 mmol/mmol for CR and < 9·7 mmol/24 h for CE. The resulting diagnostic specificities would be 0·351, 0·021 and 0·320, respectively. This means that 64·9%, 97·9% and 68·0%, respectively, of the PHPT patients would be sampled together with the FHH patients. The co-sampling of PHPT patients is significantly lower when using the CCCR or the CE compared to the CR, with 2 P-values of < 0·01 (CCCR versus CR) and < 0·01 (CE versus CR). However, the co-sampling of PHPT patients did not differ significantly between the CCCR and the CE, 2P= 0·64 (CCCR versus CE). The table shows that a decrease in the percentage of effectively sampled FHH patients would result in a lower diagnostic sensitivity and fewer co-sampled PHPT patients.

In the case of 95% efficacy for FHH, the CCCR did not sample significantly fewer PHPT patients than the CE (2P = 0·051, CCCR versus CE) or the CR (2P= 0·053, CCCR versus CR). When CR and the CE were compared with each other (2P = 0·989), there was no significant difference. At nearly all fixed FHH sample sizes, CCCR performed better than CR and CE in co-sampling fewer PHPT patients. However, a cut-off point of CCCR < 0·01 for FHH without subsequent CASR gene analysis would sample only 65% of the FHH patients and misclassify 4% of the PHPT patients as having FHH. It would leave 33% of the PHPT patients with CCCR between 0·010 and 0·020, and 35% of the FHH patients undiagnosed due to a CCCR ≥0·010.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

1.5.3 Unit costs

The unit costs of tests for diagnostic testing were presented to aid committee discussion.

Table 4: Cost of diagnostic testing

Test	Unit cost	Source	Notes
Clinical biochemistry	£1.13	NHS Reference Costs 2016/17[16]	Clinical biochemistry is typically the category under which tests for alkaline phosphatase, phosphate and calcium would be categorised.
Vitamin D	£16.50	Filby 2014[18]	Average reported by two NHS hospitals[(b)]
PTH	£8.00	Committee estimate	Average of 12 test costs sought by the committee from laboratories in their local areas.
Urine test	£4.08	NICE Guideline NG45: Routine preoperative tests for elective surgery[42]	Using urinalysis analyser to determine urinary calcium excretion ratio

1.6 Resource impact

The recommendations made by the committee based on this review are not expected to have a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

One study showed that 24 h renal calcium excretion (CE) (mmol, measured directly in the urine) had a sensitivity of 87%, and a corresponding specificity of 72.2% for discriminating between patients with familiar hypocalciuric hypercalcaemia (FHH) and patients with PHPT (n=54 FHH; n=97 PHPT; Very Low quality).

One study showed that 24 h renal calcium/creatinine excretion ratio (CR) (mmol/mmol, cut-off point <0.52) had a sensitivity of 88.9 % and a corresponding specificity of 81.4% for discriminating between patients with familiar hypocalciuric hypercalcaemia (FHH) and patients with PHPT (n=54 FHH; n=97 PHPT; Very Low quality). One study showed that calcium/creatinine clearance ratio (CCCR) (cut-off point <0.0115) had a sensitivity of 79.6% and a corresponding specificity of 87.6% for discriminating between patients with familiar hypocalciuric hypercalcaemia (FHH) and patients with PHPT (n=54 FHH; n=97 PHPT; Very Low quality).

No evidence was identified for ionised calcium, phosphate, alkaline phosphatase, vitamin D, and bone turnover markers.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 Recommendations

Diagnosis and assessment

Diagnostic testing

Albumin-adjusted serum calcium measurement

B1. Measure albumin-adjusted serum calcium for people with any of the following features, which might indicate primary hyperparathyroidism:

- symptoms of hypercalcaemia, such as thirst, frequent or excessive urination, or constipation
- osteoporosis or a previous fragility fracture (for recommendations on assessing the risk of fragility fracture in people with osteoporosis see the NICE guideline on osteoporosis)
- a renal stone[a]
- an incidental finding of elevated albumin-adjusted serum calcium (2.6 mmol/litre or above).

B2. Do not measure ionised calcium when testing for primary hyperparathyroidism.

B3. If the person's albumin-adjusted serum calcium level is 2.6 mmol/litre or above, or 2.5 mmol/litre or above with features of primary hyperparathyroidism, repeat the albumin-adjusted serum calcium measurement at least once. Base the decision to carry out further repeat measurements on the level of albumin-adjusted serum calcium and the person's symptoms.

B4. Be aware that chronic non-differentiated symptoms, such as fatigue or depression, might indicate primary hyperparathyroidism and consider measuring albumin-adjusted serum calcium.

Parathyroid hormone measurement

B5. Measure parathyroid hormone (PTH) for people whose albumin-adjusted serum calcium level is:

[a] See the NICE guideline on renal and ureteric stones: assessment and management (publication expected December 2018).

- 2.6 mmol/litre or above on at least 2 separate occasions **or**
- 2.5 mmol/litre or above on at least 2 separate occasions and primary hyperparathyroidism is suspected.

B6. When measuring PTH, use a random sample and do a concurrent measurement of the albumin-adjusted serum calcium level.

B7. Do not routinely repeat PTH measurement in primary care.

B8. Seek specialist advice if:

- PTH is above the midpoint of the reference range and primary hyperparathyroidism is suspected **or**
- PTH is below the midpoint of the reference range and the concurrent albumin-adjusted serum calcium level is 2.6 mmol/litre or above.

B9. Do not offer further investigations for primary hyperparathyroidism if:

- PTH is within the reference range but below the midpoint of the reference range **and**
- the concurrent albumin-adjusted serum calcium level is below 2.6 mmol/litre.

B10. Look for alternative diagnoses, including malignancy, if PTH is below the lower limit of the reference range.

Vitamin D measurement

B11. For people with a probable diagnosis of primary hyperparathyroidism, measure vitamin D and correct any deficiency.

Excluding familial hypocalciuric hypercalcaemia

B12. To differentiate primary hyperparathyroidism from familial hypocalciuric hypercalcaemia, measure urine calcium excretion using any one of the following tests:

- 24-hour urinary calcium excretion
- renal calcium:creatinine excretion ratio
- calcium:creatinine clearance ratio.

Assessment after diagnosis

B13. For people with a confirmed diagnosis of primary hyperparathyroidism:

- assess symptoms and comorbidities
- measure eGFR (estimated glomerular filtration rate) or serum creatinine
- do a DXA (dual-energy X-ray absorptiometry) scan of the lumbar spine, distal radius and hip
- do an ultrasound scan of the renal tract.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.2 The outcomes that matter most

The committee considered the following criteria of specificity, sensitivity, positive and/or negative predictive value, or area under Receiver Operating Characteristic (ROC) curve for the index test for primary hyperparathyroidism for decision making. The committee deemed both sensitivity and specificity as equally important for decision-making.

No relevant diagnostic test accuracy studies of index tests PTH, ionised calcium, phosphate (morning vs fasting vs random test), alkaline phosphatase, vitamin D and bone turnover markers in people under investigation for suspected primary hyperparathyroidism were identified.

1.9.2.1 The quality of the evidence

There was evidence from one study evaluating the discriminative power of calcium creatinine excretion ratio (CR), 24-hour renal calcium/creatinine clearance ratio (CCCR) and 24-hour renal calcium excretion (CE) for the separation between familial hypocalciuric hypercalcaemia and primary hyperparathyroidism.

The evidence for all outcomes was graded Very Low quality due to risk of bias and indirectness, as the included population had a confirmed diagnosis of primary hyperparathyroidism. These limitations were taken into account by the committee when interpreting the evidence.

1.9.2.2 Benefits and harms

Evidence from one study reported sensitivity, specificity and area under curve (AUC) for the tests CR, CCCR and CE for the diagnosis of familial hypocalciuric hypercalcaemia. The optimal cut-off point for diagnosing familial hypocalciuric hypercalcaemia patients using CCCR was < 0·0115 and this value had a diagnostic specificity of 0·88 and a sensitivity of 0·80. The optimal cut-off values for 24-hour CE was 5·45 mmol with a sensitivity of 0·870 and specificity of 0·722 and 24-hour CR and the optimal cut-off values for CR was 0·52 mmol/mmol, with a sensitivity of 0·889 and specificity of 0·814. The committee agreed that all three tests performed equally accurately in the diagnosis of familial hypocalciuric hypercalcaemia.

1.9.3 From the AUCs it appeared that CCCR gives a marginally better discrimination between familial hypocalciuric hypercalcaemia and primary hyperparathyroidism than CR and CE. The committee acknowledged that AUCs compare test accuracy over different thresholds for positivity and provide information on overall measure of the performance of the test, but in actuality these tests are usually employed at one given threshold and therefore the sensitivity/specificity at that particular threshold are more useful markers of how good the test will be in clinical practice.

1.9.4 Cost effectiveness and resource use

No relevant economic evaluations were identified for this question. Unit costs were presented to the committee for consideration.

NHS reference costs (2015–16) lists the pathology cost for clinical biochemistry (which typically includes test for calcium) to be £1.13. A urine test (using urinalysis analyser) was estimated to be £4.08 based on prices of necessary equipment as listed in the NHS supply chain catalogue and staff time according to the Personal Social Services Research Unit (PSSRU). The cost of the test for vitamin D was estimated to be £16.50, using numbers reported in a previous study which averaged the reported price from two hospitals.

The cost of PTH was estimated using a number of values reported by committee members from their experience with laboratories. While we were unable to obtain individual prices from each lab, a range of between £6.50 and £10.20 for around 12 labs was given, with an approximate average of £8.00. The committee considered these costs and agreed they reflected those used in real practice, and that there will be some variation between practices. This is notably more expensive than that for a general clinical biochemistry test including calcium, therefore the committee considered it important that the recommendations did not lead to excessive testing for PTH.

Firstly, the committee considered it important to repeat an albumin-adjusted serum calcium test to confirm that an initial elevation in serum calcium level was repeated prior to PTH testing due to the intra-individual variability in calcium levels. As the cost of a clinical biochemistry test (including that for calcium) is relatively low, the committee considered it important that there is confirmation of hypercalcaemia with a repeat albumin-adjusted serum calcium level before a more expensive PTH test was ordered. The committee considered a repeat test for calcium could potentially be cost-saving if it lowers the number of unnecessary tests for PTH. The committee also noted that if results for repeated tests for albumin-adjusted serum calcium are consistently high, but the result for PTH test is not high, it could be an indicator for more serious conditions including cancer. Hence, the committee deemed it important to have a contemporaneous calcium test alongside the PTH test.

Secondly, the committee considered it important to have different recommendations for those with different calcium levels. The committee noted that the prevalence of primary hyperparathyroidism in those with an albumin-adjusted serum calcium level of 2.6mmol/litre and over is high. The main differential diagnosis here is cancer and a PTH serves to make the distinction between the common cause of PTH-independent hypercalcaemia, cancer, and PHPT. The committee regarded the checking of PTH as part of current practice in all patients with sustained hypercalcaemia.

The committee discussed that the prevalence of primary hyperparathyroidism in those with an albumin-adjusted serum calcium of 2.5mmol/litre and above is lower and therefore testing for PTH is more likely to lead to a greater proportion of unnecessary PTH testing in those who do not have primary hyperparathyroidism and hence incur a high cost. Therefore the committee considered it important that in people with albumin-adjusted serum calcium above 2.5mmol/litre, only those with a clinical suspicion of primary hyperparathyroidism have a PTH test.

The committee also discussed that the costs incurred when a diagnosis of primary hyperparathyroidism is missed could be high if the patient experiences a clinical event, such as fragility fracture and renal stones, as a result of untreated primary hyperparathyroidism, the costs of which are much higher than those associated with diagnostic tests.

The committee discussed that current practice for diagnostic testing for primary hyperparathyroidism is widely variable. They considered that if practice for sequencing of tests for albumin-adjusted serum calcium and PTH is standardised in this way, this may present an area for cost saving.

Overall, the committee noted that excessive testing in the process of diagnosing primary hyperparathyroidism should be avoided where possible. However, this should not have precedence over the importance of achieving a timely and accurate diagnosis. Thresholds for testing should be considered alongside patient history and symptoms by the relevant healthcare provider.

1.9.5 Other factors the committee took into account

Based on their experience, the committee agreed that albumin-adjusted serum calcium level is an appropriate first-line biochemical test in those with suspected hypercalcemia. The committee were aware that there are several equations, however each laboratory need to take into account their methods for calcium and albumin and their population mean for those values rather than adopting a 'fixed' equation. Laboratories should regularly review what is happening to their correction calculation. The committee noted that albumin-adjusted serum calcium measurement could be done with or without a cuff as it would not make any difference in the values as it is albumin adjusted.

In the experience of the committee it is not necessary to measure ionised calcium. They noted that this test cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. The committee felt that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory based tests. Furthermore the sample has to be handled very quickly, making it a less reliable test.

The committee discussed that there was a significant inter-individual variability in calcium levels, for example biological variation for calcium is 2.1%; and 2.2% for albumin; and the population variability for calcium is 2.5%. The committee stated that the normal reference range for serum calcium as defined by Association of Clinical Biochemistry and Laboratory Medicine is 2.2–2.6 mmol/litre. The committee discussed that repeat calcium testing was performed for the purpose of validation and also to get a contemporaneous serum calcium value along with PTH, but not for diagnostic information. The committee noted that the frequency of repeat calcium testing is context and convenience driven. How often to repeat the test depends on a number of different factors including the levels of calcium reported and symptomatology.

Based on their clinical experience, the committee recommended performing a PTH test for people with an albumin-adjusted serum calcium level repeatedly 2.6mmol/litre or above, because they are more likely to have hypercalcaemia, which is a strong indicator of primary hyperthyroidism. The committee noted that a second measurement of albumin-adjusted serum calcium was useful, as along with intra-individual and population variability, there could be external causes such as inaccuracy and imprecision of instruments which could lead to variation in the serum calcium values.

For people with an albumin-adjusted serum calcium level repeatedly 2.5mmol/litre or above and where clinical suspicion of hypercalcaemia is high due to symptoms the committee recommended performing a PTH test. The committee agreed that not all symptoms are specific to primary hyperparathyroidism. There is a small group of patients with primary

hyperparathyroidism in whom the calcium may be within the normal range (normocalcaemia) and these patients would fall under the above category. The committee however noted that the vast majority of presentations of primary hyperparathyroidism are in people with hypercalcaemia.

The committee discussed that if someone has had an incidental finding of elevated albumin-adjusted serum calcium, the albumin-adjusted serum calcium test should be repeated and if it remains elevated PTH testing should be offered. The committee recognised that repeat calcium testing will reduce the number of unnecessary PTH tests. The committee felt that repeating the calcium test is necessary due to random error or changes in the level of physiologically active calcium because of alterations in blood pH or serum albumin. The committee agreed that this test could be performed either in a primary or a secondary care setting.

The committee agreed that those patients with raised albumin-adjusted serum calcium and PTH above the mid-point of the reference range would need specialist advice regarding a likely diagnosis of primary hyperparathyroidism.
The committee discussed that there is ambiguity around the PTH lower cut-off and as to when primary hyperparathyroidism is ruled out. Hence, they felt that in people with hypercalcaemia and PTH below the lower limit of the reference range, alternative causes for hypercalcaemia must be sought. The committee noted that the most common cause of hypercalcaemia with a suppressed PTH is malignancy, but other non-malignant causes such as granulomatous conditions (for example sarcoidosis), and endocrine conditions (for example thyrotoxicosis) may be involved. Thus, such patients need to be investigated and referred appropriately. The committee noted that specialist referral in this context could be an oncologist, endocrinologist, endocrine surgeon etc. The committee from their experience highlighted that there could be a small proportion of primary hyperparathyroidism patients in whom the PTH levels are in the lower part of the reference range.

The committee agreed that for people with a PTH below the midpoint of the reference range and repeated albumin-adjusted serum calcium 2.6 mmol/litre or above, specialist advice should be sought for further investigations for primary hyperparathyroidism. It was recognised that lower concentrations of PTH can be seen in rare cases of PHPT.

The committee agreed that for people with a PTH within the reference range but below the midpoint of the reference range and albumin-adjusted serum calcium less than 2.6 mmol/litre, no further investigation for PHPT is required as they are unlikely to have PHPT. The committee felt that in such cases the GP could consider further investigations for alternative diagnoses if the clinical picture suggested underlying pathology.

The committee stated that PTH testing can be done on a random sample, i.e. non-fasting and at any time of day. The committee felt that even though there is a marginal diurnal variation in PTH levels, it is not large enough to be adjusted for. It was also agreed that the PTH test does not need to be repeated prior to referral. The committee noted that the reference range for PTH varies from lab to lab, so numerical thresholds cannot be specified in the recommendation. The committee also noted that there was a huge inter-individual variability for this test. The committee felt that PTH testing should be done with contemporaneous albumin-adjusted serum calcium testing, as it is necessary to interpret the PTH result in the context of the albumin-adjusted serum calcium level.

The committee discussed the importance of assessment of vitamin D status in all patients with primary hyperparathyroidism. They highlighted that 25-hydroxy vitamin D testing is not required to diagnose primary hyperparathyroidism; however vitamin D deficiency should be explored in all patients with primary hyperparathyroidism as it leads to an increase in the amount of PTH that is secreted, increase in the severity of bone disease, and could also lead to higher post-operative risk. The committee agreed that 25-hydroxy vitamin D should be

measured to fully assess primary hyperparathyroidism and also to ensure that people with primary hyperparathyroidism are rendered vitamin D replete. The committee suggested that this test could be performed either in a primary or secondary care setting. The committee noted that treatment of vitamin D deficiency in patients with primary hyperparathyroidism usually has little effect on serum calcium levels but is associated with a reduction in PTH. The committee accepted that treatment for vitamin D deficiency would continue post-diagnosis of primary hyperparathyroidism to ensure vitamin D is replete in the long term.

The committee discussed that the PTH and albumin-adjusted serum calcium tests are performed at first presentation; hence these tests could be performed in either primary or secondary care.

The committee discussed that in people with hypercalcaemia, when PTH is elevated or within the upper part of the reference range, primary hyperparathyroidism is the most likely diagnosis but familial hypocalciuric hypercalcaemia should be considered. In this condition, urinary calcium/creatinine ratio is low and other members of the family may have hypercalcaemia. Though familial hypocalciuric hypercalcaemia has similar biochemical features to primary hyperparathyroidism, it generally requires no treatment and therefore it is important to exclude familial hypocalciuric hypercalcaemia prior to consideration of any treatment particularly surgery. The committee felt that urine calcium excretion tests were important discriminatory tests and hence based on their experience and evidence from the small study agreed to recommend the following tests for discriminating primary hyperparathyroidism from familial hypocalciuric hypercalcaemia: 24-hour urinary calcium excretion, renal calcium/creatinine excretion ratio and calcium/creatinine clearance ratio. Evidence was available for these tests conducted at 24 hours. The committee acknowledged that there was no evidence for urine calcium excretion performed on a spot urine sample or at 2 hours, but they felt that these would not be different from the tests conducted at 24 hours; hence did not specify any time points for performing the above tests. The committee discussed that the purpose of these tests is to avoid surgery in people who will not benefit from surgery. The committee agreed that the literature is inconsistent about the thresholds for these tests and hence did not recommend any specific thresholds. The committee from their experience discussed that in practice not all three tests are offered, but one of the tests (usually calcium creatinine excretion ratio) is performed.

The committee discussed that if the above calcium/creatinine ratio tests are positive then these patients would undergo further genetic testing for definitive diagnosis of familial hypocalciuric hypercalcaemia and thus spare patients with familial hypocalciuric hypercalcaemia from unnecessary surgical treatment. If these tests are false negative, then these patients would undergo unnecessary surgery and it would result in ‘failed surgery’ as these patients do not have primary hyperparathyroidism. If these tests are false positive, patients undergo genetic analysis for confirmation and surgery would have been delayed in such patients.

The committee agreed that all patients with a confirmed diagnosis of primary hyperparathyroidism will need baseline assessment of their symptoms, eGFR/serum creatinine, BMD by DXA scan of lumbar spine, distal radius and hip and ultrasound of the renal tract to help determine the optimal management pathway.

The committee decided not to recommend phosphate as a separate test, as phosphate is not part of ‘pooled’ biochemistry testing. The committee’s opinion was that phosphate testing was not used as much now as in the past because of the improvement in PTH assays, however this test may be helpful in distinguishing primary hyperparathyroidism from other causes, for example cancer.

The committee decided not to recommend alkaline phosphatase, as it is part of pooled testing and, in any case, was not considered to be of help in establishing the diagnosis of primary hyperparathyroidism.

The committee discussed that there are a number of different genetic tests available and ways they can be performed and this is outside the scope of this guideline; hence they did not make a separate recommendation on these tests. The committee highlighted that these tests were important in assessment of other endocrine conditions such as multiple endocrine neoplasia (MEN).

The committee acknowledged a potential role of bone turnover markers, but due to lack of evidence decided not to recommend, but drafted a research recommendation for the test. The committee discussed that current practice involved using DXA scans to assess fracture risk, but it would be useful to know if bone turnover markers could be used as a surrogate marker for fracture risk. The committee noted that theoretically bone turnover markers could be better than DXA scans in assessing fracture risk.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 5: Review protocol: diagnostic tests**

Field	Content
Review question	Which biochemical test or combination of tests should be used for diagnosing primary hyperparathyroidism (for example levels of parathyroid hormone, blood calcium and phosphate, alone or in combination)?
Type of review question	Diagnostic
Eligibility criteria – population	Adults (18 years and over) with suspected primary hyperparathyroidism due to one of the following: • presenting with hypercalcaemia (adjusted serum calcium above 2.6mmol/L) with or without symptoms. • presenting with an adjusted serum calcium level within the reference range (2.2-2.6mmol/L) but would be suspected to have PHPT due to end-organ damage or an incidental raised PTH level. These people would have suspected normocalcaemic PHPT. Population strata: • Presenting with hypercalcaemia versus normocalcaemia • Pregnant women with suspected PHPT Exclusions: • patients under 18 years old • general population screening (patients not suspected to have PHPT due to one of the above reasons) • established diagnosis of PHPT
Eligibility criteria – index tests	It is a given that the next test in someone with a raised adjusted serum calcium should be serum parathyroid hormone (PTH) assay (alongside an adjusted serum calcium) (to diagnose PHPT and rule out alternative diagnoses such as cancer). However, the way in which the PTH test should be performed (e.g. time of day) and the threshold at which to diagnose PHPT is not a given. These factors are also not a given in people with suspected normocalcaemic PHPT. Therefore, in people with suspected PHPT (due to one of the above two reasons set out in the population section), we will: • Assess the accuracy of morning PTH, fasting PTH and random PTH • Find the optimal threshold for the diagnosis of PHPT (trade-off between over and under referral to secondary care). The above will be in a primary care setting. We also want to investigate whether any additional tests (in addition to serum adjusted calcium and serum PTH) should be performed to improve the accuracy of the diagnostic 'work-up' to identify people with PHPT. Therefore, we will assess the accuracy of adding the following tests to the diagnostic work-up: • Ionised calcium • Phosphate (morning versus fasting versus random test) • Urinary calcium excretion (24 hour urine calcium versus spot urine calcium) • Alkaline phosphatase • Vitamin D

	• Calcium/creatinine clearance ratio (CCCR) (calculated from simultaneous determinations of plasma levels and 24-h renal excretions of calcium and creatinine) • Calcium/creatinine excretion ratio (calculated from simultaneous determinations of serum and urine levels of calcium and creatinine) • 24 hour (urine) calcium/creatinine excretion ratio, mmol/mmol • 24 hour (renal) calcium excretion, mmol per 24 hours • Bone turnover markers
Eligibility criteria –reference (gold) standard	PHPT diagnosed by histology following parathyroidectomy (histology includes a descriptive characterisation of cell type and conclusion of parathyroid adenoma). Reference standard for FHH – gene mutation analysis
Outcomes and prioritisation	Target condition: primary hyperparathyroidism Outcomes for test and treat review: • Mortality • Quality of life • Number of people receiving treatment, i.e., including people who may not have needed it such as those with false positive results) • Repeat testing / additional testing • Timing • Adverse events related to test (as reported in the papers) • Adverse events related to treatment (as reported in the papers) • preservation of end organ function (bone mineral density, fractures, renal stones and renal function) • persistent hypercalcaemia • cardiovascular events • cancer incidence Outcomes for diagnostic accuracy review: • Specificity • Sensitivity • Positive and / or negative predictive value • ROC curve or area under curve
Eligibility criteria – study design	• RCTs (for test-and-treat) • Cross-sectional studies / cohort studies / single-gate studies (for diagnostic accuracy) Exclusion: Two gate studies
Other inclusion exclusion criteria	Exclusions: Non-English language papers Conference abstracts
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups will be examined in the following order: 1. vitamin D level (deficient (<30nmol/L) versus insufficient (30 to <50nmol/L) versus replete (≥50nmol/L)) 2. creatinine clearance (eGFR < or >30ml/min)
Selection process –	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in

duplicate screening / selection / analysis	this protocol.
Data management (software)	• Sensitivity and specificity are calculated using Cochrane Review Manager (RevMan5). • Diagnostic meta-analyses are conducted using WinBUGS14 and graphically presented using RevMan5. • Endnote for bibliography, citations, sifting and reference management
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library, CINAHL and PsycINFO Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2002 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	N/A
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10051
Highlight if amendment to previous protocol	N/A
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as Appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or G (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias is evaluated for each outcome on a study using the QUADAS-2 checklist.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment –	For details please see section 6.2 of Developing NICE guidelines: the manual.

publication bias, selective reporting bias	
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jonathan Mant in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 6: Health economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[41] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then

Review question	All questions – health economic evidence
	it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 August 2018	Exclusions
Embase (OVID)	1974 – 06 August 2018	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 8 of 12 CENTRAL to 2018 Issue 7 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 06 August 2018	Exclusions
PsycINFO (ProQuest)	Inception – 06 August 2018	Exclusions

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14

16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language

1 **Embase (Ovid) search terms**

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language

2 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Hyperparathyroidism] explode all trees
#2.	MeSH descriptor: [Hyperparathyroidism, Primary] explode all trees
#3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) near/6 (HPT or hyperparathyroidis*)):ti,ab
#4.	PHPT:ti,ab
#5.	MeSH descriptor: [Parathyroid Neoplasms] explode all trees

#6.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)):ti,ab
#7.	(or #1-#6)

CINAHL (EBSCO) search terms

S1.	(MH "Hyperparathyroidism")
S2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 HPT) OR ((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 hyperparathyroidis*)
S3.	PHPT
S4.	(MH "Parathyroid Neoplasms")
S5.	(parathyroid* n3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcemi* or hypercalcaemi*))
S6.	S1 OR S2 OR S3 OR S4 OR S5
S7.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website
S8.	S6 NOT S7

PsycINFO (ProQuest) search terms

1.	su.Exact("parathyroid neoplasms" OR "hyperparathyroidism" OR "hyperparathyroidism, primary")
2.	PHPT
3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) Near/6 (HPT or hyperparathyroidis*))
4.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcaemi* or hypercalcemi*))
5.	1 or 2 or 3 or 4
6.	(su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))
7.	(s1 or s2 or s3 or s4) NOT (su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to primary hyperparathyroidism population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics papers published since 2002.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 06 August 2018	Exclusions Health economics studies
Embase	2002 – 06 August 2018	Exclusions Health economics studies

Database	Dates searched	Search filter used
Centre for Research and Dissemination (CRD)	HTA - Inception – 06 August 2018 NHSEED - Inception to March 2015	None

1 **Medline (Ovid) search terms**

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.

38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.

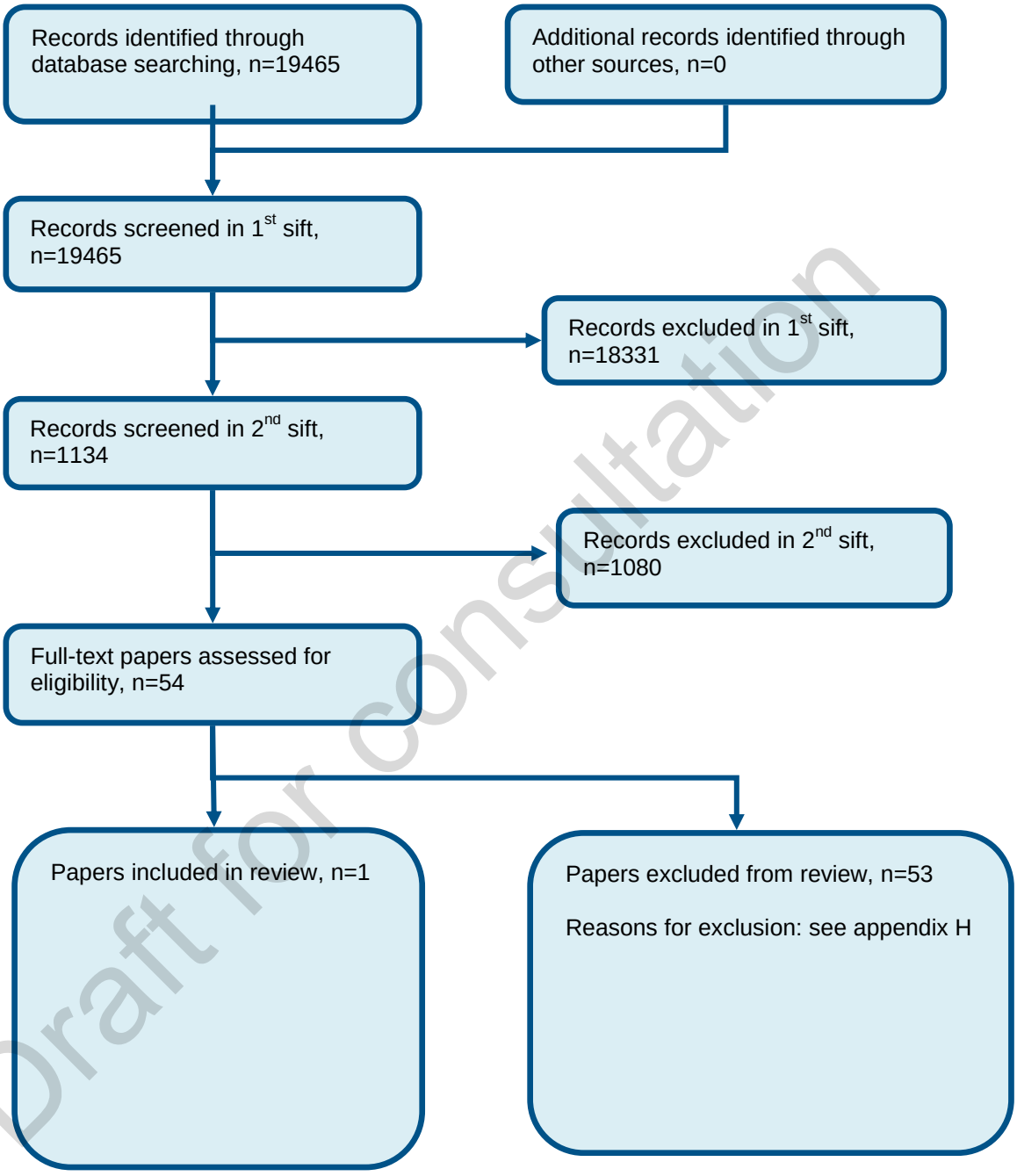
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hyperparathyroidism EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Hyperparathyroidism, Primary EXPLODE ALL TREES
#3.	(((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)))
#4.	(PHPT)
#5.	MeSH DESCRIPTOR Parathyroid Neoplasms EXPLODE ALL TREES
#6.	((parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)))
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8.	* IN NHSEED
#9.	* IN HTA
#10.	#7 AND #8
#11.	#7 AND #9

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of diagnostic tests



Appendix D: Clinical evidence tables

Reference	**Christensen, 2008** [13]
Study type	Cross-sectional study
Study methodology	Data source: database Recruitment: From August 2003 to April 2007, 54 hypercalcaemic (mean of up to three measurements of albumin-adjusted calcium) patients with familiar hypocalciuric hypercalcaemia (FHH) a clinically significant mutation in the CASR gene and no clinical signs of parathyroid adenoma as judged by combined single photo emission computed tomography (SPECT) and planar parathyroid (Tc-sestamibi) and thyroid (Tc) scintigraphy and ultrasonography were included. In 21 FHH kindreds, 14 participants were index patients and 40 were diagnosed by subsequent family screening. In three of the 14 index patients it was not possible to identify hypercalcaemic family members. To minimise the exposure to radiation, the family members were not subjected to radionuclear scintigraphy. FHH patients were compared with 97 patients with PHPT .All PHPT patients were hypercalcaemic (mean of up to three measurements of albumin-adjusted calcium) with elevated or high normal plasma PTH. The upper 1/3 of the normal reference range was included because plasma PTH depends on the vitamin D status in the reference population. Only 3.7% of the FHH patients (n=54, median=57 nmol/l; range=18-154) and only 6.1% of the PHPT patients (n=66, median =61nmol/l, range 12-169 nmol/l) had a 25 OHD level below 25 nmol/l, that is vitamin D deficiency. The PHPT patients all underwent parathyroid surgery, leading to normocalcaemia 2 months after surgery. Histopathological examination revealed adenomas in 84 of the patients, hyperplasia in 11 and combined adenoma and hyperplasia in 2 of the patients.
Number of patients	n = 54 FHH; n=97 PHPT
Patient characteristics	Age: FHH: 18-75 years; PHPT: 19-86 years Gender (male to female ratio):FHH: 17 males and 37 females ;PHPT: 17 males and 80 females Ethnicity: not stated Country: Denmark Among the FHH patients 13/54=24% [95% CI 12.7-35.5%] had elevated plasma PTH (average of up to three measurements) compared with 86/97=89% (95% CI 82.4-95%) of the patients with PHPT. The FHH patients had significantly lower median values

Reference	**Christensen, 2008** [13]
	for plasma creatinine, plasma PTH and all three indices of renal calcium handling and higher plasma phosphate levels than the PHPT. Inclusion criteria: Patients with PHPT; patients with FHH Exclusion criteria: for both patient groups were reduced renal function (plasma creatinine>140 µmol/l), other calcium metabolic or bone diseases, lithium treatment, systemic glucocorticoid treatment for more than 6 months, malignant disease, uncontrolled or newly diagnosed chronic disease, and hospital admission due to drug or alcohol abuse.
Target condition(s)	PHPT; FHH
Index test(s) and reference standard	Index test(s) 1. 24 h renal calcium excretion (CE, mmol, measured directly in the urine) 2. 24 h renal calcium/creatinine excretion ratio (CR, mmol/mmol) calculated as :CR= 24 h renal calcium/24h renal creatinine excretion 3. Calcium /creatinine clearance ratio (CCCR) calculated as: CCCR= (24 h U-calcium/P-calcium, total)/ (24-h U-creatinine/P-creatinine) with variables entered as mmol or mmol/l. Reference standard Histopathological findings at neck exploration leading to normocalcaemia in all PHPT cases. The gold standard for FHH- genetic studies confirming a clinically significant mutation in all FHH patients.
Statistical measures	Index texts Receiver operating characteristic (ROC) curve analysis for discrimination between patients with FHH and patients with PHPT. Cut-off points are for the diagnosis of FHH AUC SE Cut-off point Sensitivity Specificity 2P CE 0.867 0.029 <5.45 0.870 0.722 0.50* CR 0.903 0.027 <0.52 0.889 0.814 0.56** CCCR 0.923 0.021 <0.0115 0.796 0.876 0.19*** 2P denotes significance of differences between area under the curves (AUCs): * CE vs CR, ** CR vs CCCR, *** CCCR vs CE From the AUC's it appears that CCCR gives a marginally better discrimination between FHH and PHPT than CR and CE. However

Reference	Christensen, 2008 [13]

the AUCs were not significantly different, with p-values of 0.50 (CE vs CR), 0.56 (CR vs CCCR), and 0.19 (CCCR vs CE). The optimal cut-off point for diagnosing FHH patients suing CCCR in a one-step diagnostic procedure was <0.0115. This value returns a diagnostic specificity of 0.88 and a sensitivity of 0.80. The optimal cut-off values for 24h CE and 24 CR were 5.45 mmol and 0.52 mmol/mmol, respectively.

Overlap analysis: (Post-hoc)

Sampling	≤ 85% FHH	Sampling ≤ 90% FHH	Sampling ≤ 95% FHH	Sampling 100% FHH
CE				
Cut-off	< 5·4	< 6·6	< 8·0	< 9·7
Sensitivity	0·833	0·889	0·944	1
Specificity	1–0·268 = 0·732	732 1–0·412 = 0·588	1–0·546 = 0·454	1–0·680 = 0·320
PHPT sample	26/97 = 26·8%	40/97 = 41·2%	53/97 = 54·6%	66/97 = 68·0%
CR				
Cut-off	< 0·52	< 0·57	< 0·75	< 1·84
Sensitivity	0·833	0·889	0·944	1
Specificity	1–0·186 = 0·814	1–0·268 = 0·732	1–0·443 = 0·557	1–0·979 = 0·021
PHPT sample	18/97 = 18·6%	26/97 = 26·8%	43/97 = 44·3%	95/97 = 97·9%
CCCR				
Cut-off	< 0·014	< 0·018	< 0·019	< 0·027
Sensitivity	0·833	0·889	0·944	1

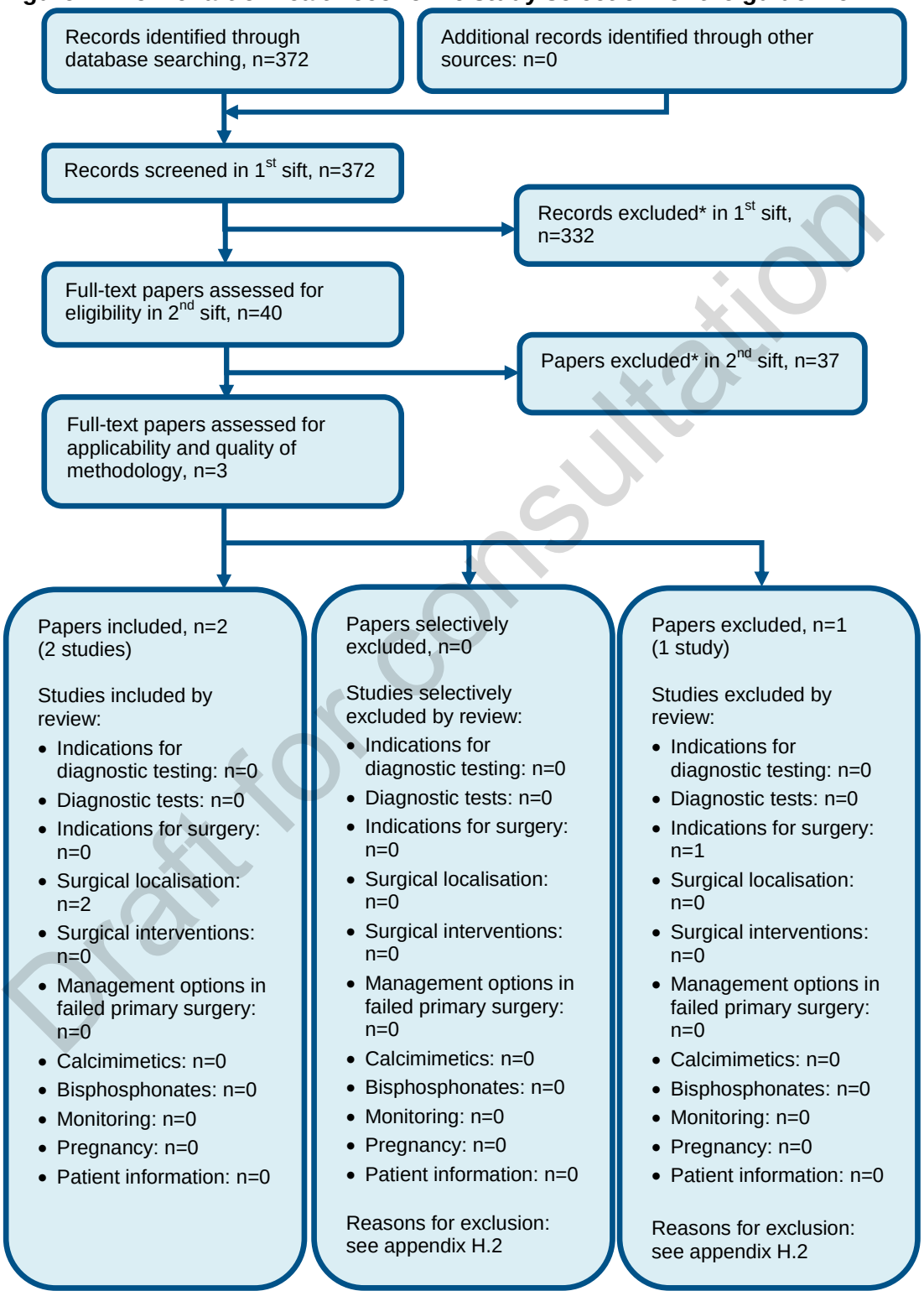
Reference	**Christensen, 2008** [13]
	Specificity 1–0·175 = 0·825 1–0·309 = 0·691 1–0·309 = 0·691 1–0·649 = 0·351 PHPT sample 17/97 = 17·5% 30/97 = 30·9% 30/97 = 30·9% 63/97 = 64·9% Overlap performance analysis disclosed that the CCCR included fewer patients with PHPT together with the FHH patients than the other two variables at different cut-off points. The overlap performance analyses for the three variables of renal calcium handling using fixed FHH sample sizes showed that- to sample 100% of all patients with FHH (diagnostic sensitivity = 1), a cut-off point of < 0·027 should be used for CCCR, < 1·84 mmol/mmol for CR and < 9·7 mmol/24 h for CE. The resulting diagnostic specificities would be 0·351, 0·021 and 0·320, respectively. This means that 64·9%, 97·9% and 68·0%, respectively, of the PHPT patients would be sampled together with the FHH patients. The co-sampling of PHPT patients is significantly lower when using the CCCR or the CE compared to the CR, with 2 P-values of < 0·01 (CCCR vs. CR) and < 0·01 (CE vs. CR). However, the co-sampling of PHPT patients did not differ significantly between the CCCR and the CE, 2P= 0·64 (CCCR vs. CE). Results showed that a decrease in the percentage of effectively sampled FHH patients would result in a lower diagnostic sensitivity and fewer co-sampled PHPT patients. In the case of 95% efficacy for FHH, the CCCR did not sample significantly fewer PHPT patients than the CE (2P = 0·051, CCCR vs. CE) or the CR (2P= 0·053, CCCR vs.CR). When CR and the CE compared with each other (2P = 0·989), there was no significant difference. At nearly all fixed FHH sample sizes, CCCR performed better than CR and CE in co-sampling fewer PHPT patients. However, a cut-off point of CCCR < 0·01 for FHH without subsequent CASR gene analysis would sample only 65% of the FHH patients and misclassify 4% of the PHPT patients as having FHH. It would leave 33% of the PHPT patients with CCCR between 0·010 and 0·020, and 35% of the FHH patients undiagnosed due to a CCCR ≥0·010.
Source of funding	Not stated
Limitations	Indirectness: the included population was with a confirmed diagnosis of PHPT
Comments	Most of the patients in the study had adenoma, not hyperplasia, as seen in some cases of FHH.

Appendix E: Coupled sensitivity and specificity forest plots and sROC curves

None.

Appendix F: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Health economic evidence tables

No economic studies were included in this review.

1 Appendix H: Excluded studies

H.1 2 Excluded clinical studies

3 **Table 9: Studies excluded from the clinical review**

Reference	Reason for exclusion
Amal 2004[1]	Inappropriate index test. Study evaluated the intact PTH determination by an automated immunoassay using chemiluminescence.
Attie 1983[2]	Inappropriate index test. Study evaluated the role of parathyroid hormone in the relative hypocalciuria of FHH.
Benson 1987[3]	No useable outcomes
Bergenfelz 1991[4]	No useable outcomes
Bhatti 2000[5]	No useable outcomes. Incorrect study design – not diagnostic study.
Black 2013[6]	No useable outcomes. The study aimed to establish whether urinary and serum calcium levels are co-related in patients with PHPT.
Blind 1998[7]	Incorrect index test – study compared the utility of measurements of serum intact human PTH and mid region human PTH in patients with disorders of extracellular calcium metabolism.
Borresen 1981[8]	Incorrect study design
Boudou 2005[9]	Inappropriate comparison. Study compares 2 second-generation PTH assays with 2 third-generation assays in PHPT patients.
Broadus 1981[10]	No useable outcomes
Brown 1987[11]	Inappropriate study design and intervention – study describes a direct immunoassay for circulating intact human PTH.
Canary 1969[12]	Review – screened for references
Christensen 2009[14]	Follow-up study of Christensen 2008 [13] already included in the review
Christensen 2011[15]	Review. Screened for relevant references.
Dunegan 1974[17]	Incorrect study design – study reports pre-operative evaluation and co-relation with surgical findings in patients with PHPT
Fillee 2012[19]	Inappropriate index test – study uses 2-site second-generation immunochemiluminescent assay
Fisken 1981[20]	No appropriate index test – the study assessed the relative importance of different causes of hypercalcaemia
Forster 1988[21]	No useable outcomes
Frolich 1993[22]	Inappropriate index test – alarm filter was to differentiate between clinically significant and clinically non-significant hypercalcaemia
Gao 2001[23]	Incorrect index test. Study evaluates a novel immunoradiometric assay which specifically measures biologically active whole PTH (1-84). The assay is based on a solid phase coated with anti-PTH (39-84) antibody, a tracer of 125I-labeled antibody with a unique specificity to the first N-terminal amino acid of PTH (1-84).
Gibb 1990[24]	No useable outcomes

Reference	Reason for exclusion
Gunn 1992[25]	No appropriate reference standard for FHH
Hackeng 1985[26]	No useable outcomes
Higashi 1985[27]	Incorrect index test. Study evaluated usefulness of the chloride/phosphate ratio for distinguishing primary hyperparathyroidism from hypercalcemia due to other causes.
Inaba 2004[28]	Incorrect index test and comparison. Study compares Bio-Intact parathyroid hormone (1– 84) assay (Bio-PTH), a newly developed two-site immune chemiluminometric assay to second-generation “intact PTH” (I-PTH) assays for parathyroid hormone.
Jayasena 2011[29]	No useable outcomes
Jin 2012[30]	No useable outcomes
Kent 1987[31]	No appropriate index test
Kvarstein 1983[32]	Incorrect study design. Wrong tests (and not in conjunction with calcium/PTH tests).
Lo Cascio 1978[33]	No appropriate index test
Lyons 1986[34]	No appropriate index test
Marx 1981[35]	No appropriate index test
Marx 1981[36]	No appropriate index test
McLeod 1984[37]	No useable outcomes
Misiorowski, 2012[38]	Inappropriate index test – bone densitometry
Mismar, 2013[39]	Incorrect index test. Study examined the sensitivity of chloride/phosphate ratio with a cut-off point of >33 as a diagnostic test for PHPT.
Monchik 1980[40]	No useable outcomes.
Newman 1988[43]	No appropriate index test – C-terminal and N-terminal PTH
Ong 2012[44]	Insufficient information to calculate sensitivity and specificity
Robinson 1990[45]	Inappropriate study design – case series
Ruda 2005[46]	Systematic review – did not include diagnosis methods specified in our protocol
Shinall 2013[47]	Literature review – screened for relevant references
Shishiba 1987[48]	Inappropriate index test. First-generation PTH radioimmunoassay.
Sorensen 2012[49]	Inappropriate population
Souberbielle 2017[50]	Review: references checked
St. John 1988[51]	Incorrect index test and comparison – study compares intact assay with conventional radioimmunoassay for carboxy terminal PTH
Strott 1967[52]	No useable outcomes
Stuckey 1987[53]	No useable outcomes

Reference	Reason for exclusion
Taha 2011[54]	No appropriate index test. Study evaluated the prevalence of low calcium excretion in African American patients with PHPT.
Tee 2013[55]	No useable outcomes
Transbol 1977[56]	Inappropriate index test – study evaluates the relative efficiency of four methods of serum calcium determination in the detection of hypercalcemia in hyperparathyroidism
Watanabe 1983[57]	Inappropriate study design – case series. No useable outcomes.
Wibell 1972[58]	Incorrect study design. Wrong tests.

H.2 Excluded health economic studies

None.

Appendix I: Research recommendations

I.1 Bone turnover markers

Research question: What is the clinical utility of bone turnover markers in the diagnosis and management of primary hyperparathyroidism?

Why this is important:

Bone turnover markers are a surrogate index of skeleton involvement in primary hyperparathyroidism (PHPT). In current practice the treatment thresholds for PHPT for bone health, namely a fragility fracture or osteoporosis, are likely to be relatively late outcomes from bone demineralisation. The aim is to investigate whether mainstream bone turnover markers that are primarily used in the setting of osteoporosis (in addition to serum adjusted calcium and serum PTH) would improve the accuracy of the diagnostic 'work-up' to identify people with PHPT; to identify patients who could benefit from surgical treatment earlier than is currently offered and explore the role of bone markers in the follow up of patients who have had surgical treatment.

An evidence review was conducted but no relevant studies were identified. Hence no recommendations could be made on bone turnover markers in the guideline.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults (18 years and over) with suspected primary hyperparathyroidism due to one of the following: a) presenting with hypercalcaemia (adjusted serum calcium above 2.6mmol/L) with or without symptoms. b) presenting with an adjusted serum calcium level within the reference range (2.2-2.6mmol/L) but would be suspected to have PHPT due to end-organ damage or an incidental raised PTH level. These people would have suspected normocalcaemic PHPT. Intervention(s): Bone turnover markers + Serum calcium + PTH (parathyroid hormone) Comparison: Serum calcium + PTH Outcome(s): Health-related quality of life, mortality, preservation of end organ function (bone mineral density, fractures, renal stones and renal function), persistent hypercalcaemia, cardiovascular events, adverse event and cancer incidence.
Importance to patients or the population	The aim is to investigate the clinical utility of serum bone turnover markers (in addition to serum adjusted calcium and serum PTH) in the management of PHPT. 1) Identification of patients with increased bone turnover may identify patients who could benefit from surgical treatment earlier than is currently offered. 2) An exploration of the role of bone markers in the follow up of patients who have had surgical treatment may identify a sub group of patients whose bone health requires further additional active management. 3) Detailed multivariant analysis of bone markers with other biochemical and outcome parameters could identify interactions with other clinical drivers and improve outcomes.
Relevance to NICE guidance	This research will reduce the existing uncertainty in determining current surgical treatment thresholds. The research will reduce the variation in the management of patients with normocalcaemic hyperparathyroidism. Currently this entity is only actively managed once end organ damage, such as renal tract stones, has occurred. The treatment thresholds for bone health, namely a fragility fracture or osteoporosis, are likely to be relatively late outcomes from

	bone demineralisation. The potential for earlier intervention will be explored. The research will assess the clinical effectiveness and cost-effectiveness of serum bone marker assays. There is currently no evidence in a UK based study on which to base recommendations. It will enable future guidelines to clearly recommend an evidence based approach to the clinical utility of these tests in this group of patients.
Relevance to the NHS	By correctly assessing people and treating appropriately patient outcomes should be improved, reducing the need to access health resource. Equally, information would be obtained on the cost, necessity and benefit of bone turnover markers which would then inform decisions on whether testing should be performed in the NHS.
National priorities	No
Current evidence base	No evidence was identified.
Equality	No
Study design	Systematic review of diagnostic test and treat studies.
Feasibility	The time scale will need to be 24–60 months to ensure adequate follow-up so that differences in interventions can be seen between the groups.
Other comments	Currently DXA scans are used to assess fracture risk, but the committee felt that it would be useful to know if bone turnover markers could be used as a surrogate marker for fracture risk. The committee noted that theoretically bone turnover markers could be better than DXA scans in assessing fracture risk.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.