National Institute for Health and Care Excellence

Draft for consultation

Hyperparathyroidism (primary): diagnosis, assessment and initial management

[A] Evidence review(s) for indications for diagnostic testing

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: What are the indications for diagnostic testing for primary hyperparathyroidism?

1.2 Introduction

Primary hyperparathyroidism (PHPT) is usually diagnosed as a result of investigation of hypercalcaemia. Hypercalcaemia is often picked up as an incidental finding on a blood test, though in some cases, a blood test is done because of a clinical suspicion of hypercalcaemia, which is associated with specific symptoms such as thirst and frequent urination. While people with PHPT may be asymptomatic, some may experience many different symptoms including depression, tiredness and constipation. Some people with PHPT develop renal stones and some may experience fractures due to low bone mineral density or osteoporosis.

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) presenting with the following symptoms (or a combination of these symptoms) (symptoms as defined in the study): • fatigue • depression • muscle weakness • constipation • stomach pain • loss of concentration • mild confusion • an incidental abnormal blood test result Exclusions: • patients under 18 years old • general population screening (healthy people without any symptoms) • established diagnosis of PHPT
Eligibility criteria – index tests	Symptoms: • fatigue • depression • muscle weakness • constipation • stomach pain • loss of concentration • mild confusion • an incidental abnormal blood test result • neurocognitive
Eligibility criteria – reference (gold) standard	• Clinical decision to treat as PHPT • PHPT diagnosed by histology following parathyroidectomy / biochemical cure
Outcomes	Target condition: primary hyperparathyroidism

	Specificity Sensitivity Positive and / or negative predictive value ROC curve or area under curve
Study design	Cross sectional studies, cohort studies (including both retrospective and prospective analyses) 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)

1.4 Clinical evidence

A search was conducted for studies in people presenting with symptoms of primary hyperparathyroidism. The aim of the review was to identify the indications for testing for PHPT, including symptoms and any incidental blood test results. The review was planned to evaluate the accuracy of non-specific symptoms (or combinations of symptoms) for identifying whether PHPT is present (sensitivity and specificity).

1.4.1 Included studies

No clinical evidence was identified for this question.

See also the study selection flow chart in appendix C and study evidence tables in appendix D.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.5 Review question: In adults with fragility fracture, renal stones, and/or renal tract calcification what is the incidence of primary hyperparathyroidism?

For full details see the review protocol in appendix A.

Table 2: PICO characteristics of review question

Population	People with fragility fracture, renal stones, renal tract calcification
Target condition	• fragility fracture • renal stones • renal tract calcification
Outcomes	Diagnosis of PHPT
Study design	Prospective cohort studies Retrospective cohort studies will be included only if insufficient prospective cohort studies are identified Key confounders: PHPT – fractures • Age

	• Sex • Family history of early hip fracture • Previous fractures PHPT – renal stones/calcifications • Previous stones

1.6 Clinical evidence

1.6.1 Included studies

A search was conducted for observational studies in people with fragility fracture, renal stones and/or renal tract calcification and the objective was to determine the incidence of PHPT in this population. People who have had a clinical event are not consistently being tested for raised calcium, hence the aim of the review was to identify if people with a clinical event should be tested to see if they currently have PHPT.

Seven studies were included in the review: Bergstrom 2006 [7]; Di Monaco 2004 [30]; Fuss 1987 [41]; Kim 2018[60]; Sharma 2017[85] Walker 2013 [95]; Wikstrom 1983 [96]; these are summarised in Table 3 below. One study was in patients with forearm fracture (RCT); one in patients with hip fracture (comparative cohort); 3 studies in patients with renal stones (non-comparative) and 2 studies in patients with urolithiasis (one comparative and one non-comparative cohort) with no evidence of adjustment for confounding variables. None of the studies adjusted for key confounders.

The clinical evidence could not be meta-analysed due to the nature of the outcome/data; hence the results were presented separately according to the variables (fractures, renal stones) identified in the protocol.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 4, Table 5 and Table 6). See also the study selection flow chart in appendix C, study evidence tables in appendix D, GRADE tables in appendix F and excluded studies list in appendix I.

1.6.2 Excluded studies

See the excluded studies list in appendix I.

1.6.3 Summary of clinical studies included in the evidence review

Table 3: Summary of studies included in the evidence review

Study	Intervention and comparison	Prognostic variable	Outcomes	Comments
Bergstrom 2006[7] RCT Sweden	n= 168 Post-menopausal women between 45 and 65 years of age with a forearm fracture. Inclusion criteria: Previous forearm fracture and BMD in the interval -1 to -3.0 119 women age 58.9 (50-65) years of age with 9.5 (1-19) years since last menstruation met the BMD criteria for inclusion. Their BMI was 24.7 (19.9-31). Of these 20 were osteoporotic (T-score <-2.5) and 99 had osteopenia (T-score from -1 to 2.4). Their BMD values measured (g/cm): L2.L4, 1.001 (0.813-1.354); femoral neck, 0.835 (0.680-1.129).	Forearm fracture	Prevalence of PHPT in this population	Serum creatinine, calcium, alkaline phosphatase and urine samples were taken for glucose and albumin. A medical examination and, when appropriate, additional lab tests to rule out secondary causes were performed. PTH was analysed in individuals with hypercalcaemia.
Di Monaco 2004[30] Prospective cohort study Italy	n=450 patients with original hip fracture either spontaneously or as a result of minimal trauma. n=444 (404 postmenopausal women, and 40 men) sex matched subjects, aged 65	Hip fracture	Diagnosis of PHPT	The diagnosis of PHPT was established when both serum calcium adjusted for serum albumin exceeded the normal range and PTH was either elevated or high normal.

Study	Intervention and comparison	Prognostic variable	Outcomes	Comments
	years and older who were referred for their first osteodensitometry were studies as controls.			
Fuss 1987[41] Prospective cohort study Belgium	n=1433 Renal stone formers systematically referred from A&E departments irrespective of the severity of their disease and the level of serum calcium.	Renal stones	Diagnosis of PHPT	When serum calcium was persistently 2.58 mmol/l or more and other causes of hypercalcaemia had been excluded, primary hyperparathyroidism was thought to be highly probable and exploration of the neck was proposed to the patient.
Kim 2018[60] Retrospective cohort study South Korea	n=925 urolithiasis patients hospitalised at a single institute from 2013 to 2016.	Urolithiasis	Diagnosis of PHPT	PHPT was diagnosed when serum intact PTH was higher than the normal range without evidence of vitamin D deficiency or chronic kidney disease. Diagnosis of PHPT compared with the estimated diagnosis of PHPT in urolithiasis patients in the general South Korean population from 2013 to 2016.
Sharma 2017 [85] Prospective cohort study India	n=381 urolithiasis patients; mean age (SD) 38.5 (13.9)	Urolithiasis	Diagnosis of PHPT	Diagnosis of PHPT was based on the following criteria: serum Ca ≥10.2 mg/dL with clearly elevated (>70 pg/mL) or nonsuppressed iPTH (>25 pg/mL) or elevated iPTH but normal serum Ca after exclusion of secondary PHPT and histologically confirmed parathyroid adenoma or hyperplasia
Walker 2013[95]	n=1983 men and n=816	Renal stones	Number of patients with	Diagnosis of PHPT not defined.

Study	Intervention and comparison	Prognostic variable	Outcomes	Comments
Retrospective cohort study UK	women Patients investigated in the Renal stones clinic of the Department of Clinical Biochemistry, from June 1990 to March 2007 without exclusions.		PHPT	
Wikstrom 1983 [96] Prospective cohort study Sweden	n=389 Renal stone formers investigated in an out-patient stone clinic.	Renal stones	Patients diagnosed with PHPT	Diagnosis of PHPT was based on demonstration of sustained hypercalcaemia and verified at surgery.

See appendix D for full evidence tables.

1.6.4 Quality assessment of clinical studies included in the evidence review

Table 4: Clinical evidence summary: Patients with hip fracture versus controls (observational comparative studies)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
Diagnosis of PHPT	888 (1 study)	LOW[a] due to risk of bias	RR 4.20 (1.60 to 11.04)	Among the hip fracture patients 21/444 (4.7%) fulfilled the diagnostic criteria of PHPT. Among the controls, 5/444 (1.13%) fulfilled the diagnostic criteria of PHPT.

[a] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.

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2 **Table 5: Clinical evidence summary: Patients with renal stones/urolithiasis (observational studies)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
Diagnosis of PHPT	1433 (1 study)	LOW[a] due to risk of bias	-	Overall: 23/1433 (1.6%) Men: 11/977 (1.1%) Women: 12/456 (2.6%)
	925 (1 study)	LOW[a] due to risk of bias	-	urolithiasis patients: 4/925 (0.4%) patients with urolithiasis in the general population: 341/85,267 (0.4%)*
	381 (1 study)	LOW[a] due to risk of bias	-	19/381 (5%) **
	389 (1 study)	LOW[a] due to risk of bias	-	14/389 (3.5%)
	2799 (1 study)	LOW[a] due to risk of bias		Overall: 74/2274 (3.2%) Women: 29/747 (4%) Men: 45/1787 (2.5%)

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

*Study reports estimated diagnosis of PHPT among urolithiasis patients in the general population of South Korea

** This was reported to be 10 to 20 times higher than the prevalence of PHPT in the general population

3 **Table 6: Clinical evidence summary: Post-menopausal women with distal forearm fracture (RCT)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
Diagnosis of PHPT	119 (1 study)	LOW[a]	-	8/119 (6.7%)*

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
		due to risk of bias		

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

* Study reports that the prevalence of PHPT was three times higher than previously observed in earlier studies on healthy Swedish post-menopausal women

1.7 Economic evidence

1.7.1 Included studies

No relevant health economic studies were identified.

1.7.2 Excluded studies

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

See also the health economic study selection flow chart in appendix G.

1.7.3 Unit costs

Table 7: Cost of diagnostic testing

Test	Unit cost	Source	Notes
Calcium	£1.13	NHS Reference Costs 2016-17[28]	Cost of clinical biochemistry test, of which calcium is often a component.
Vitamin D	£16.50	Filby 2014[39]	Average reported by two NHS hospitals
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[76]	Using urinalysis analyser to determine urinary calcium excretion

1.8 Resource costs

The recommendations made by the committee based on this review may have a substantial impact on resources. While costs of the individual tests are relatively low, the size of the population potentially affected will be large. Hence, where they represent a change in practice additional costs may be incurred.

1.9 Evidence statements

1.9.1 Clinical evidence statements

Evidence from one study (n=888, low quality) suggested that among the hip fracture patients, a higher percentage of patients (4.7%) fulfilled the diagnostic criteria of PHPT compared with patients without hip fracture (1.13%).

Evidence from five studies (n=5,927; Low quality) suggested that among patients with renal stones/urolithiasis, 0.4%-5% met the diagnostic criteria of PHPT.

Evidence from one study (n=119, Low quality) suggested that among post-menopausal women with distal forearm fracture 6.7% met the diagnostic criteria of PHPT.

1.9.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.10 Recommendations

Diagnosis and assessment

Diagnostic testing

Albumin-adjusted serum calcium measurement

A1. 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).

A2. Do not measure ionised calcium when testing for primary hyperparathyroidism.

A3. 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.

A4. Be aware that chronic non-differentiated symptoms, such as fatigue or depression, might indicate primary hyperparathyroidism and consider measuring albumin-adjusted serum calcium.

1.11 The committee's discussion of the evidence

1.11.1 Interpreting the evidence

1.11.1.1 The diagnostic measures that matter most

For review question 1.1 the committee considered the following criteria of specificity, sensitivity, positive and/or negative predictive value ROC curve or area under curve for the index tests/symptoms (fatigue, depression, muscle weakness, constipation, stomach pain,

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

loss of concentration, mild confusion, an incidental abnormal blood test result, neurocognitive) for primary hyperparathyroidism for decision making.

For review question 1.2 the committee considered diagnosis of primary hyperparathyroidism as a critical outcome for decision making. There were no other outcomes identified in the protocol for this review question.

1.11.1.26 The quality of the evidence

No clinical evidence was identified for review question 1.1.

For review question 1.2 there were 7 studies included in the review; one study was in patients with forearm fracture (RCT); one in patients with hip fracture (comparative cohort study) and 3 studies in patients with renal stones (non-comparative cohort study) and 2 studies in patients with urolithiasis (one comparative and one non-comparative cohort study). The aim of the review was to determine whether people with the above conditions should be tested for hypercalcaemia and primary hyperparathyroidism.

All evidence was of low quality due to risk of bias. No evidence was available for patients with renal tract calcification.

The committee acknowledged the limited quality and number of studies included in this review.

1.11.1.38 Benefits and harms

The clinical evidence could not be meta-analysed due to the nature of the outcome/data; hence the results were presented separately according to the variables (fractures, renal stones) in the studies.

The evidence suggested that among the hip fracture patients, 4.7% fulfilled the diagnostic criteria of primary hyperparathyroidism compared to 1.13% with primary hyperparathyroidism in patients without hip fracture; among patients with renal stones/urolithiasis 0.4%-5% met the diagnostic criteria of primary hyperparathyroidism and among post-menopausal women with distal forearm fracture 6.7% met the diagnostic criteria of primary hyperparathyroidism.

Due to the low quality of the evidence, the committee also took their clinical experiences into account when making their recommendations.

The committee discussed that people with symptoms of hypercalcaemia such as thirst, polyuria and/or constipation should have albumin-adjusted serum calcium testing, as primary hyperparathyroidism is a common cause of raised calcium levels. The committee noted that there were other non-PTH related causes of hypercalcaemia such as malignancy, granulomatous conditions like, sarcoidosis and tuberculosis, drugs like thiazide diuretics, AIDS etc. The committee agreed that albumin-adjusted serum calcium testing is an appropriate first-line biochemical test in those with long duration of non-specific, particularly multi-system symptoms, and the level of albumin-adjusted serum calcium would prompt further investigations for primary hyperparathyroidism (see the recommendations on diagnostic tests).

From clinical experience, the committee noted that most patients with PHPT are discovered to have hypercalcemia incidentally on routine blood tests, but there are a group of patients where PHPT is discovered due to skeletal or renal complications.

The committee discussed that a moderately high prevalence of primary hyperparathyroidism in patients with renal stones and fractures (fragility fractures) suggest that primary hyperparathyroidism enhances the risk of these clinical events. Hence they agreed that people with such conditions would also require albumin-adjusted serum calcium testing to explore possible hypercalcaemia and primary hyperparathyroidism. The committee agreed

that although kidney stone formation due to primary hyperparathyroidism is not common, it is important to test for hypercalcaemia as quicker diagnosis and management of primary hyperparathyroidism would lead to a reduction in kidney stone risk over time. The committee hence referred to the serum calcium testing recommendation from NICE's guideline on renal stones.

Primary hyperparathyroidism is associated with bone involvement – bone turnover is reversibly increased in primary hyperparathyroidism and bone mineral density is decreased, especially in areas dominated by cortical bone. From experience, the committee stated that there was increased fracture incidence in PHPT. The committee discussed that people with any previous fragility fracture and osteoporosis (see NICE's guideline on osteoporosis: assessing the risk of fragility fracture) are at an increased risk of fracture; hence it is important that these people must be tested for hypercalcaemia as a marker of primary hyperparathyroidism.

The committee agreed that hypercalcaemia testing in people with renal stones and in those with an increased risk of fragility fractures would lead to earlier diagnosis and management of primary hyperparathyroidism as appropriate.

The committee discussed the various non-specific symptoms associated with primary hyperparathyroidism such as fatigue, depression, abdominal pain, constipation, muscle weakness, loss of concentration, and mild confusion. The committee pointed out that these symptoms are valid clinically and important from the patient perspective, but they acknowledged that there could be multiple causes for such symptoms and not all of the patients with such symptoms would have primary hyperparathyroidism. However the committee recognised that there is a need to raise awareness that symptoms such as fatigue and depression are not uncommon with a diagnosis of primary hyperparathyroidism and albumin-adjusted serum calcium testing should be done on a case-by-case basis in such patients. The committee agreed that there is uncertainty whether there is a causal link between these symptoms and PHPT.

1.1.12 Cost effectiveness and resource use

No previously published economic evaluations were identified for indications for diagnostic testing. Unit costs were presented to the committee for consideration of cost effectiveness of testing for primary hyperparathyroidism in different populations.

The cost of a clinical biochemistry test (that includes testing serum calcium) is also the lowest cost test at £1.31. The co-opted clinical biochemist for the guideline also noted that if a clinical biochemistry blood test was already being undertaken for another reason, the cost of adding the analysis of serum calcium would be even lower, estimated to be around £0.30. As mentioned in the benefits and harms section above, as there is a high prevalence of primary hyperparathyroidism in patients with hypercalcaemia, the committee considered that serum calcium testing was the most appropriate first-line test. Consequently, the committee determined that if people were to present with symptoms of hypercalcaemia, it is important that albumin-adjusted serum calcium is measured in these patients as this helps to identify a population most likely to have primary hyperparathyroidism.

Due to the low quality evidence for people with a fragility fracture or who have been diagnosed with a renal stone, the committee was unable to make a definitive judgement on the cost effectiveness of testing for hypercalcaemia in these patients from this review. However, the committee noted that in the renal stones guideline it was considered good practice that serum calcium be tested in people who have had a renal stone and should therefore be considered as part of stone analysis. Therefore it was agreed to cross-refer to this recommendation in this guideline.

Through consensus, the committee also considered it to be good practice to test albumin-adjusted serum calcium in those who have an elevated fracture risk. The committee noted

that in some cases, an initial test for calcium may already be done as part of a bone profile test in people who have an elevated risk of fracture.

Although the cost effectiveness of testing in these populations could not be formally assessed, the committee considered that testing albumin-adjusted serum calcium in these populations would help provide a timely diagnosis for those with underlying primary hyperparathyroidism. With timely treatment this could improve quality of life, as well as prevent future high cost admissions from further end organ damage such as fractures or renal stones. Detecting raised serum calcium may also be a trigger for diagnosis of other pathologies, such as cancer. Rarely, hypercalcaemia may be the first presentation of an otherwise occult cancer.

Due to the lack of strong evidence of any causal association between non-specific symptoms and primary hyperparathyroidism, the committee could not assess the cost effectiveness of testing for primary hyperparathyroidism in these patients. The committee acknowledged that despite the low cost of testing serum calcium, as these symptoms were non-specific the potential population size for testing could be very large and therefore could have a substantial resource impact if testing were to be recommended in all people with such symptoms. Due to a lack of both clinical and cost effectiveness evidence, the committee was only able to make an advisory recommendation for people presenting with these symptoms.

Overall, the committee considered that the recommendations made could lead to a change in practice for some NHS providers. The committee considered that there could be increased demand for primary care services due to increased awareness of the possible symptoms of PHPT among care providers. The committee considered that it is largely standard practice to test albumin-adjusted serum calcium in people who have osteoporosis or had a fragility fracture or renal stone. However, testing for symptoms that are non-specific or non-differentiating of hypercalcaemia – such as thirst or fatigue – are less common and thereforemay have an impact on primary care through increased demand on services. However, committee consensus was that such testing could help diagnose and therefore treat primary hyperparathyroidism earlier and therefore reduce the number of fragility fractures and renal stones associated with having primary hyperparathyroidism. Therefore, overall the committee considered thatthe actual impact of these recommendations on primary care is unlikely to be substantial. Although there is a low cost of testing for serum calcium, these recommendations apply to a large population. However, due to the uncertainty in the uptake of these recommendations, the impact on resource use is uncertain.

1.1.13 Other factors the committee took into account

The committee discussed that the main causes of hypercalcemia are primary hyperparathyroidism and malignancy and they were aware of the NICE guideline on suspected cancer: recognition and referral.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 8: Review protocol: Indications for diagnostic testing (diagnostic)**

Field	Content
Review question	What are the indications for diagnostic testing for primary hyperparathyroidism?
Type of review question	Diagnostic
Objective of the review	The aim is to identify the indications for testing for PHPT, including symptoms and any incidental blood test results. Which symptoms and/or incident test results should indicate when someone should receive further biochemical testing for suspected PHPT. The way this will be investigated is by evaluating the accuracy of non-specific symptoms (or combinations of symptoms) for identifying whether PHPT is present (sensitivity and specificity).
Eligibility criteria – population	Adults (18 years and over) presenting with the following symptoms (or a combination of these symptoms) (symptoms as defined in the study): • fatigue • depression • muscle weakness • constipation • stomach pain • loss of concentration • mild confusion • an incidental abnormal blood test result Exclusions: • patients under 18 years old • general population screening (healthy people without any symptoms) • established diagnosis of PHPT
Eligibility criteria – index tests	Symptoms: • fatigue • depression • muscle weakness • constipation • stomach pain • loss of concentration • mild confusion • an incidental abnormal blood test result • neurocognitive
Eligibility criteria – reference (gold) standard	Clinical decision to treat as PHPT PHPT diagnosed by histology following parathyroidectomy / biochemical cure
Outcomes and prioritisation	Target condition: primary hyperparathyroidism Specificity Sensitivity

Field	Content
	Positive and / or negative predictive value ROC curve or area under curve
Eligibility criteria – study design	Cross sectional studies, cohort studies (including both retrospective and prospective analyses) 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)
Other inclusion exclusion criteria	Exclusions: Non-English language papers Conference abstracts
Proposed sensitivity / subgroup analysis, or meta-regression	Sub-groups: Primary care vs secondary care Prior investigations done vs no prior investigations
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote for bibliography, citations, sifting and reference management • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library, CINAHL, 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 H (health economic evidence tables).
Methods for assessing	Standard study checklists were used to critically appraise individual

Field	Content
bias at outcome / study level	studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
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 – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
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

1 **Table 9: Review protocol: Indications for diagnostic testing (prognostic)**

Field	Content
Review question	In adults with fragility fracture, renal stones, renal tract calcification what is the incidence of PHPT?
Type of review question	Prognostic
Objective of the review	To determine whether people with the above conditions should be tested for hypercalcaemia and PHPT (calcium creatinine ratio) People who have had a clinical event are not being tested for raised calcium. This protocol covers this scenario.
Eligibility criteria – population / disease / condition / issue / domain	People with fragility fracture, renal stones, renal tract calcification

Field	Content
Prognostic variable	• fragility fracture • renal stones • renal tract calcification
Outcomes and prioritisation	Diagnosis of PHPT
Eligibility criteria – study design	Prospective cohort studies Retrospective cohort studies will be included only if insufficient prospective cohort studies are identified Key confounders: PHPT – fractures • Age • Sex • Family history of early hip fracture • Previous fractures PHPT – renal stones/calcifications • Previous stones
Other inclusion exclusion criteria	Exclusions: Non-English language papers Conference abstracts Studies with less than 50 participants.
Proposed sensitivity / subgroup analysis, or meta-regression	NA
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol
Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote for bibliography, citations, sifting and reference management • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known

Field	Content
Identify if an update	N/A
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10051
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
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 H (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 across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
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 – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
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

1

2 **Table 10: 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).[75] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then 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).

Review question	All questions – health economic evidence
	• 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.

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 11: 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	None

Database	Dates searched	Search filter used
	CENTRAL to 2018 Issue 7 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 06 August 2018	Exclusions
PsycINFO (ProQuest)	Inception – 06 August 2018	Exclusions

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

2 **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

1 **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)

2 **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

3 **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 12: 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
Centre for Research and Dissemination (CRD)	HTA - Inception – 06 August 2018 NHSEED - Inception to March 2015	None

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

1 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 Indications for diagnostic testing (diagnostic)

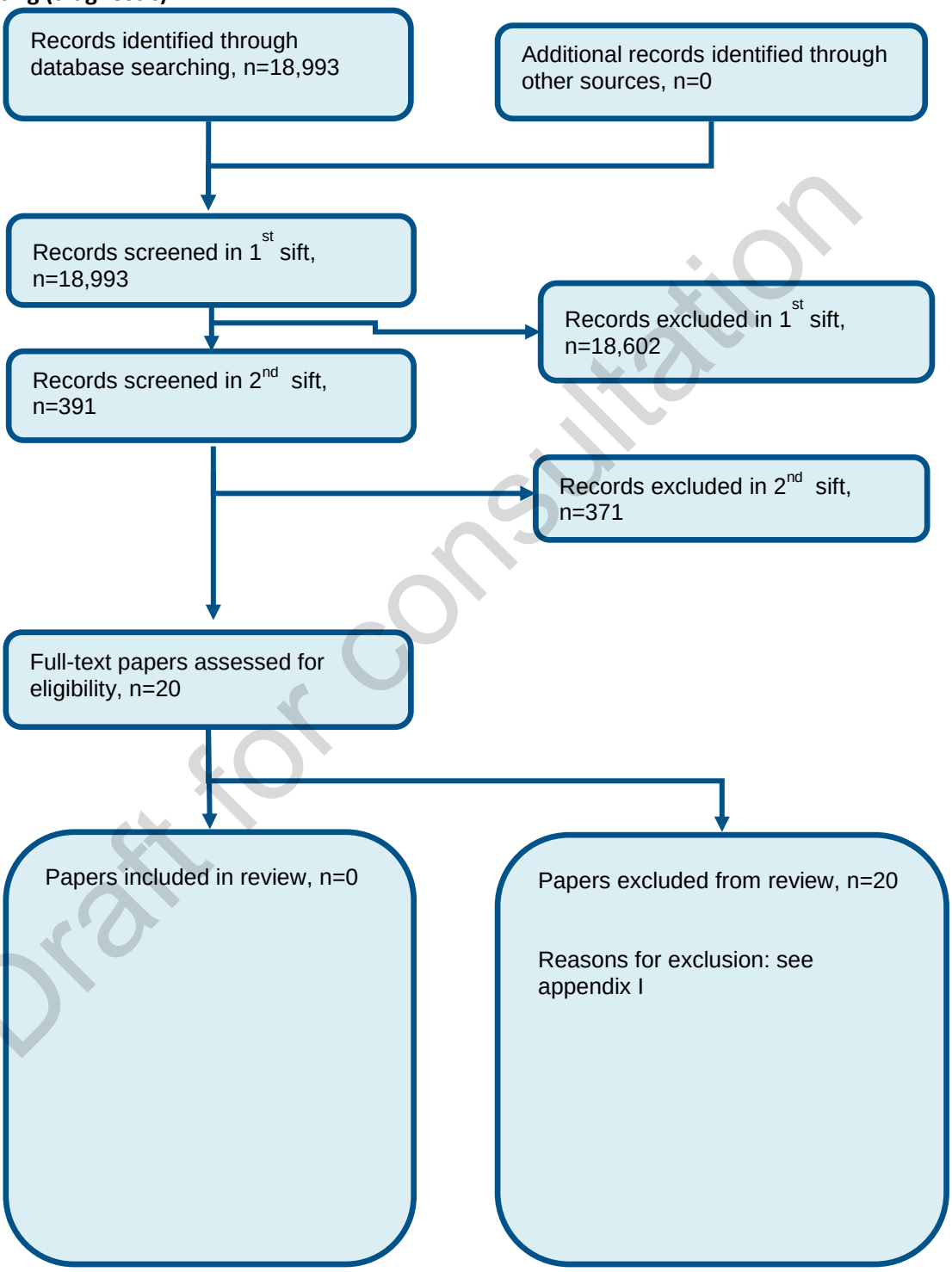
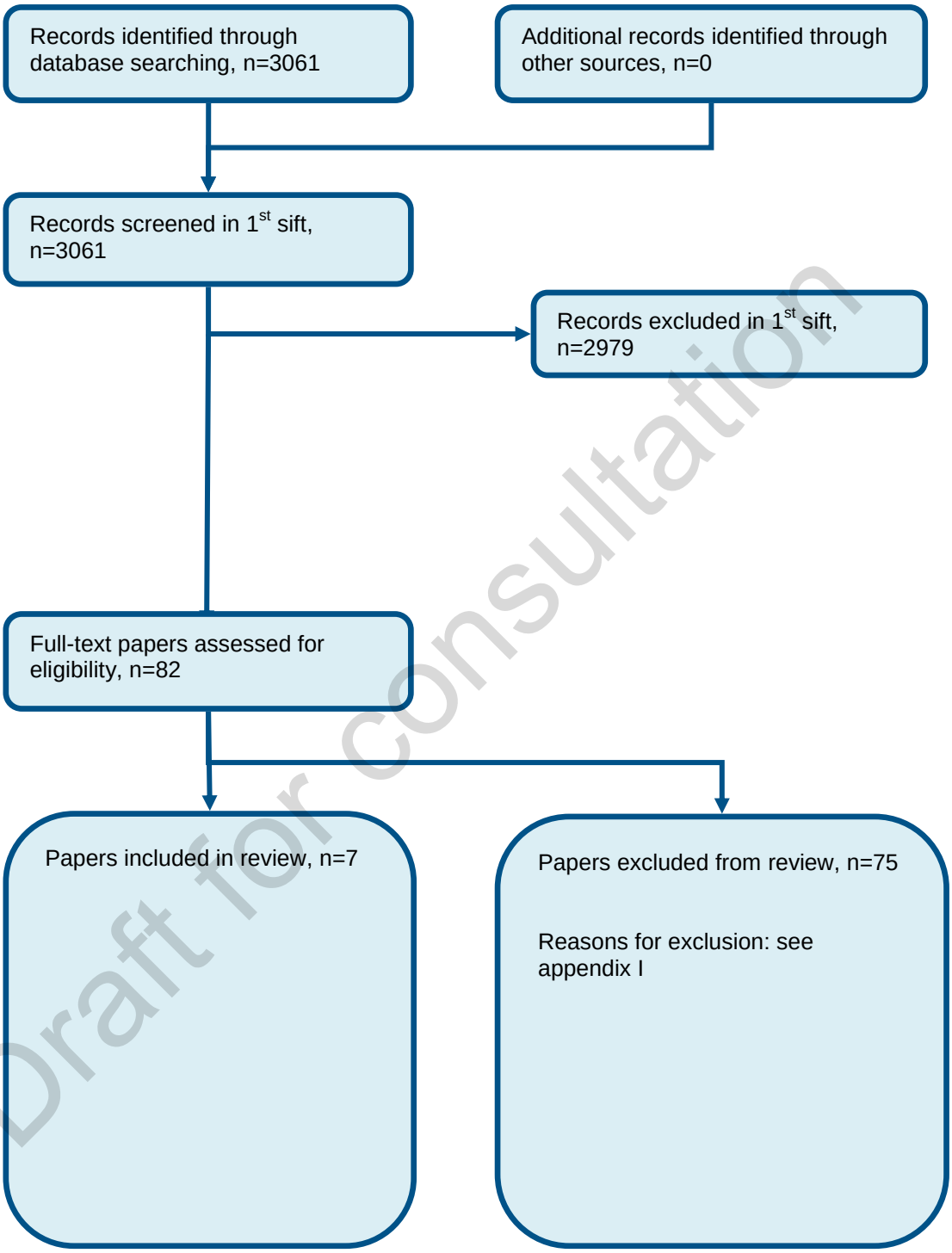


Figure 2: Flow chart of clinical study selection for the review of Indications for diagnostic testing (prognostic)



Appendix D: Clinical evidence tables

Study	Bergstrom 2006 [7]
Study type	Prospective randomised study
Number of studies (number of participants)	1 (n=119)
Countries and setting	Conducted in Sweden; Setting: hospital/community
Line of therapy	N/A
Duration of study	Not stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Previous forearm fracture and BMD in the interval -1 to -3.0.
Exclusion criteria	Medication or known diseases that could interfere with bone metabolism, low (<19.9) or high BMI (>31), treatment with antiresorptive medication or training at the level of or above that of the intervention programme (three brisk walks a week and two weight bearing training hours a week).
Recruitment/selection of patients	Postmenopausal women between 45 and 65 years of age with a wrist fracture were invited to join the study to evaluate the effect of physical training on bone mineral density.
Age, gender and ethnicity	Age (mean, range): 58.9 (50-65) Females (%): 100%
Further population details	167 women turned up for DX examination. 38 of these women had normal bone mineral density and 10 had a T-score below -3 and were excluded. 119 women age 58.9 years with 9.5 (1-19) years since last menstruation met the inclusion criteria and were called for further investigation. Of these women 20 were osteoporotic (T-score <-2.5) and 99 had osteopenia (T-score from -1 to 2.4). Their bone density values, measured (g/cm): L2.L4, 1.001 (0.813-1.354); femoral neck,0.835 (0.680-1.129). All had wrist fracture within 5 years of entering the study. 12 of these women were smokers.
Extra comments	Serum creatinine, calcium, alkaline phosphatase and urine samples were taken for glucose and albumin. A medical examination and, when appropriate, additional lab tests to rule out secondary causes were performed. PTH was analysed in individuals with hypercalcaemia.

Study	Bergstrom 2006 [7]
Indirectness of population	No indirectness
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR: POST-MENOPAUSAL WOMEN WITH WRIST FRACTURE Protocol outcome 1: Diagnosis of PHPT at end of follow-up -Actual outcome: Diagnosis of PHPT - 8/119 (6.7%) All had clear biochemical PHPT including elevated free serum calcium and inadequately high PTH, normal creatinine, and phosphate in the low normal range. Six of these were subjected to surgery. In five pathology showed parathyroid adenoma and in one patient 2 hyperplastic nodules were removed. All six patients subjected to parathyroidectomy were normocalcaemic six months after surgery. The two remaining patients were followed with regard to serum calcium and bone mass. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness. Not adjusted for key confounders.	
Protocol outcomes not reported by the study	None

1

Study	Di Monaco 2004 [30]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n= 444 hip fracture patients; n=444 controls)
Countries and setting	Conducted in Italy; Setting: rehabilitation hospital
Line of therapy	N/A
Duration of study	Not reported
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Caucasian patients who sustained an original hip fracture either spontaneously or as a result of minimal trauma (trauma equal to or less than a fall from a standing position).

Study	Di Monaco 2004 [30]
Exclusion criteria	Exclusion criteria for control patients: previous hip fractures, creatinine levels exceeding 130µM, therapy with lithium salts, and current pharmaceutical treatment for osteoporosis. No previous diagnosis of PHPT was found in the control group.
Recruitment/selection of patients	450 consecutive elderly patients admitted to a rehabilitation hospital after hip fracture were included in the study. All fractures were either spontaneous or a result of minimal trauma. N=444(404 postmenopausal women, and 40 men) sex matched subjects, aged 65 years and older who were referred for their first osteodensitometry were studies as controls.
Age, gender and ethnicity	Age: Hip fracture patients – 79.66 (8.60); controls -75.52 (5.65) Females (%): hip fracture patients- 91%; controls- 91% Baseline: Total femur BMD (T score): hip fracture patients: -2.98 (1.11); controls: -2.03 (1.09) 25-OH Vitamin D (ng/ml): hip fracture patients : 8.46 (7.8); 9.77 (8.67)
Further population details	A total of 444 hip fracture patients were included (404 menopausal women and 40 men), none of whom was currently receiving pharmaceutical treatment for osteoporosis; 15/444 receiving corticosteroids; 20/444 receiving thiazide diuretics; 18/444 receiving thyroidal hormones. None received vitamin D supplementation before blood sample collection.
Extra comments	Diagnosis of PHPT was defined as the combination of abnormally high serum calcium (adjusted for serum albumin by a conventional formula), and above normal or high normal PTH levels, in agreement with the NIH criteria. High normal values were defined as exceeding 60ng/l.
Indirectness of population	No indirectness
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIP FRACTURE PATIENTS versus CONTROLS

Protocol outcome 1: Diagnosis of PHPT
-Actual outcome: Diagnosis of PHPT : Hip fracture patients 21/444; controls 5/444

Hip fracture patients:

Only 2 of 21 underwent surgical neck exploration and both resulted in a histological diagnosis of parathyroid adenoma. None of these 21 patients was currently receiving corticosteroids or thyroidal hormones, whereas 1 patient was currently taking hydrochlorothiazide 25 mg daily.

	Hip fracture patients with PHPT (N=21)	Hip fracture patients without PHPT
Hip fracture type:	52% cervical; 48% trochanteric;	465 cervical; 54% trochanteric
Calcium (albumin adjusted; Mm):	2.70 (0.20);	2.34 (0.11)
PTH (ng/l) :	125.24 (73.76);	57.25 (43.28)

Study	Di Monaco 2004 [30]
Total femur BMD (T score): -3.33(1.35); -2.96 (1.10) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness. Not adjusted for key confounders.	
Protocol outcomes not reported by the study	None

1

Study	Fuss 1987 [41]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=1433)
Countries and setting	Conducted in Sweden ; Setting: Renal stones clinic
Line of therapy	N/A
Duration of study	Not reported
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Renal stone formers referred from Accident and Emergency Departments and from Department of Urology and Nephrology following an episode of renal colic or the discovery of renal calcification or ureteric stone, irrespective of the severity of their disease and the level of serum calcium.
Exclusion criteria	Not reported
Recruitment/selection of patients	1433 renal stone formers (977 men and 456 women) referred from A&E and Department of Urology and Nephrology were included in the study.
Age, gender and ethnicity	Age: not stated Females (%): 32%
Further population details	All patients were ambulatory and had normal states of nutrition. Serum calcium (normal range 2.25-2.63 mmol/l, 9.0-10.5 mg/dl) was measured at least twice in all patients; when it was higher than 2.5 mmol/l, additional measurements were made together with assays of serum parathyroid hormone.
Extra comments	When serum calcium was persistently 2.58 mmol/l or more and other causes of hypercalcaemia had been

Study	Fuss 1987 [41]
	excluded, primary hyperparathyroidism was thought to be highly probable and exploration of the neck was proposed to the patient.
Indirectness of population	No indirectness
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR RENAL STONE FORMERS: Protocol outcome 1: Diagnosis of PHPT -Actual outcome: Diagnosis of PHPT: 23/1433 (1.6%), 11/977 men (1.1%) and 12/456 women (2.6%). In all patients serum calcium reached 2.63 mmol/l or more on some occasion. However, 8 patients showed intermittent hypercalcaemia. Twenty patients underwent neck surgery. PHPT was confirmed in 19, including the 8 patients with intermittent hypercalcaemia. A single adenoma was found in 13 cases, 2 adenomas in 2 and diffuse hyperplasia in 4; no abnormal gland was found in 1 patient. Serum calcium, phosphate and PTH and urinary calcium returned to normal after surgery, except in the patient in whom neck exploration was unsuccessful. PHPT remained a possibility in 10 patients (8 men and 2 women) with a follow-up of 1 to 108 months; their mean serum calcium and phosphate were 2.62 (0.03) mmol/l and 0.90 (0.19) mmol/l respectively. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness. Not adjusted for key confounders.	
Protocol outcomes not reported by the study	None

1

Study	Kim 2018 [60]
Study type	Retrospective cohort study (comparative)
Number of studies (number of participants)	1 (n=925; n=85,267 urolithiasis patients of Korea)
Countries and setting	Conducted in South Korea; Setting: single unspecified institute (secondary hospital)
Line of therapy	N/A
Duration of study	4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Study	Kim 2018 [60]
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients hospitalised for treatment of urolithiasis at a single centre from January 2013 to December 2016, no further inclusion criteria were specified;
Exclusion criteria	Not reported
Recruitment/selection of patients	925 patients hospitalised for urolithiasis between 2013 and 2016 at a single institute enrolled in the study; During the same period, there were 85267 patients with urolithiasis in Korea; to obtain this longitudinal data from the Health Insurance Review and Assessment Service (HIRA) database containing the diagnosis, treatment, procedures, surgical history, and prescription drug information for 46 million patients per year were used. The South Korean population was obtained from the Korean Statistical Information Service
Age, gender and ethnicity	Age: not stated
Further population details	All cases of one gland parathyroidectomy and urolithiasis treatments from HIRA database (nationwide insurance claims database), containing the diagnosis, treatment, procedures, surgical history and prescription drug information for 46 million patients per year, accounting for 90% of the total Korean population and covering 99% of all medical claims in South Korea, were identified to obtain the number of parathyroidectomies in the general population.
Extra comments	PHPT was diagnosed when serum intact PTH was higher than the normal range without evidence of vitamin D deficiency or chronic kidney disease.
Indirectness of population	No indirectness
Funding	National Research Foundation of Korea (NRF) grant funded by the Korean government
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS in urolithiasis patients enrolled in the study and the general population Protocol outcome 1: Diagnosis of PHPT -Actual outcome: Diagnosis of PHPT: 4/925 (0.4%) Risk of bias: All domain -High, Selection -High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness. Not adjusted for key confounders. In all patients 45 showed elevated serum intact PTH, 4 of whom (3 female, 1 male) were diagnosed with PHPT and underwent subsequent parathyroidectomy. The remaining 41 patients had elevated PTH due to vitamin D deficiency (n=31) or chronic kidney disease (n=10). Protocol outcome 2: Diagnosis of PHPT (general population) -Actual outcome: Estimated diagnosis of PHPT: 341/85267 (0.4%).	

Study	Kim 2018 [60]
Not adjusted for key confounders. Narrative data: Study reports that estimated annual incidence of PHPT in general South Korean population ranged from 0.007% to 0.0014%.	
Protocol outcomes not reported by the study	None

1

Study	Sharma 2017[85]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=381)
Countries and setting	Conducted in India; Setting: not specified
Line of therapy	N/A
Duration of study	3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with urolithiasis; inclusion criteria not specified.
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients presenting with urolithiasis
Age, gender and ethnicity	Age mean (SD): 38.5 (13.9) Male; Female ratio 1.6:1
Further population details	Most patients had presented with nonspecific abdominal discomfort and were found to harbour urinary stones on ultrasound imaging of the abdomen.
Extra comments	Diagnosis of PHPT was based on the following criteria: serum Ca ≥10.2 mg/dL with clearly elevated (>70 pg/mL) or nonsuppressed iPTH (>25 pg/mL) or elevated iPTH but normal serum Ca after exclusion of secondary PHPT and histologically confirmed parathyroid adenoma or hyperplasia
Indirectness of population	No indirectness
Funding	Not specified

Study	Sharma 2017[85]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS in urolithiasis patients Protocol outcome 1: Diagnosis of PHPT -Actual outcome: Diagnosis of PHPT: 19/381 (5%); Males: 8, Females: 11; this was reported to be 10 to 20 times higher than the prevalence of PHPT in the general population. Prior history of fractures and other musculoskeletal symptoms were common in PHPT compared to those without PHPT. Four patients with PHPT had prior fractures following trivial trauma. Ureteric calculi or concurrent renal with ureteric calculi was common in PHPT compared to no PHPT. Four patients with PHPT (21.1%) and 8 patients without PHPT (2.2%) had nephrocalcinosis (P<.01). Biochemical measures: Haemoglobin was significantly lower in patients with PHPT compared to patients without PHPT (mean: 10.69, SD: 0.55 vs 12.08 SD: 0.11, P<.01). Serum Ca (mg/dL) and alkaline phosphate levels were significantly higher in patients with PHPT (Ca mg/dL mean: 11.23, SD: 0.29 vs mean; 9.34, SD: 0.04). There was no difference in urinary biochemical parameters. Four of the 19 (21%) patients with PHPT were diagnosed with normocalcaemic PHPT (NPHPT) after confirming the presence of a parathyroid adenoma at surgery. There was no significant difference in age, serum phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, or iPTH levels between patients with NPHPT (n=4) and PHPT (n=15). Predictors of PHPT: the presence of multiple stones (OR: 3.02, CI: 1.06-8.57), recurrent stones (OR: 1.90, CI: 0.74-4.87), bilateral stones (OR: 2.32, CI: 0.91-5.89) and nephrocalcinosis (OR: 11.8, CI: 3.19-43.6) predicted the presence of underlying PHPT among stone formers. The simultaneous presence of multiple (≥3 renal and ureteric stones), recurrent, or bilateral stones had an OR of 3.06 (CI: 0.87-10.7) predicting the presence of PHPT. Other symptoms/signs associated with PHPT were: nephrocalcinosis (OR: 5.34, CI: 1.09-25.93), neuropsychiatric manifestations (OR: 9.93, CI: 1.53-64.6), and proximal myopathy (OR: 8.14, CI: 1.72-38.54). Risk of bias: All domain -High, Selection -High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness . Not adjusted for key confounders.	
Protocol outcomes not reported by the study	None

1

2

Study	Walker 2013 [95]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=2799) (1983 men and 816 women)
Countries and setting	Conducted in UK; Setting: Renal stones clinic
Line of therapy	N/A
Duration of study	June 1990 to March 2007

Study	Walker 2013 [95]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Anonymised data from the first attendance to renal stones clinic
Exclusion criteria	Not stated
Recruitment/selection of patients	The clinic database was created in 1996 and included data for most patients investigated for stones risk at their initial presentation to the clinic from June 1990 to March 2007. In addition to biochemistry test results and composition of stones analysed, the records included age, sex, age of stone episode, numbers of first-degree relatives with stones, structural renal tract abnormalities, another recognised risk factor for stones, took mineral or vitamin D supplements or medications relevant to stones formation.
Age, gender and ethnicity	Age (median, mean): men- 49 (49); women 49 (49) Females (%): 816 (29%)
Further population details	847/2799 patients had produced stones on more than one occasion and were classed as recurrent stone formers.
Extra comments	NA
Indirectness of population	No indirectness
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS: Patients investigated in renal stones clinic Protocol outcome 1: Diagnosis of PHPT -Actual outcome: Patients PHPT Overall: 74/2274 (3.2%) Women: 29/747 (4%) Men: 45/1787 (2.5%) 29 (4%) of 747 women and 45 (2.5%) of 1787 men (total 74/ 2534 (3%)) with paired plasma calcium and PTH results had biochemical abnormalities consistent with PHPT (plasma calcium >2.55 mmol/l and PTH >3.0 pmol/L; >2.0 pmol/L, 2002-2003 assay) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness. Not adjusted for key confounders.	

Study	Walker 2013 [95]
Protocol outcomes not reported by the study	None

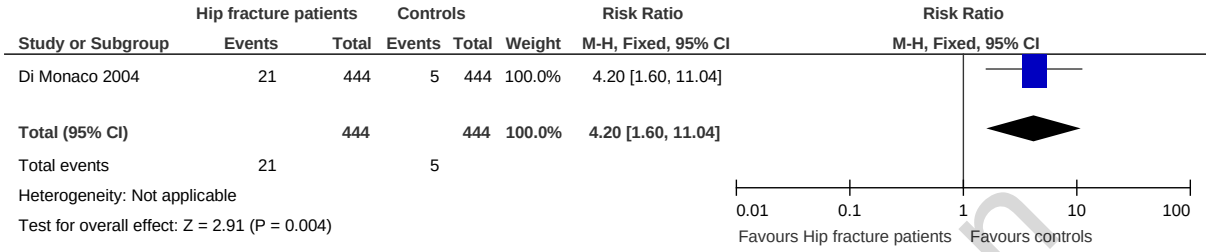
1

Study	Wikstrom 1983 [96]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=389 PHPT patients
Countries and setting	Conducted in Sweden; Setting: Out-patient renal stone clinic
Line of therapy	N/A
Duration of study	N/A
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with recurrent renal stones admitted to the out-patient renal stone clinic for diagnostic evaluation.
Exclusion criteria	Not reported
Recruitment/selection of patients	389 consecutive renal stone formers admitted to the out-patient renal stone clinic for diagnostic evaluation were included in the study. Most patients were referred from the Department of Urology and Surgery of the University hospital. Some 10% were patients from other hospitals or from general practitioners in the surrounding country.
Age, gender and ethnicity	Age (mean, range): males- 44 (13-68); females- 38 (20-69) Males: Females: 275: 114
Further population details	Onset of stone disease occurred at a mean age of 32 years (range 7-60) in males and 28 years (range 11-63) in females.
Extra comments	The patients received polyethylene bottles and instructions for collecting three 24 h urine samples at home prior to attending the clinic. No dietary advice or restrictions were given before the investigations, which were performed on an ambulatory basis. Diagnosis of PHPT was based on demonstration of sustained hypercalcaemia and verified at surgery. The diagnostic criteria for renal stone were visualisation of stone by x-ray, operation or spontaneous passage.

Study	Wikstrom 1983 [96]
Indirectness of population	No indirectness
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR RENAL STONE FORMERS: Protocol outcome 1: Diagnosis of PHPT -Actual outcome: Diagnosis of PHPT: 14/389 (3.5%) 5/14 patients had family history of renal stones Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness. Not adjusted for key confounders.	
Protocol outcomes not reported by the study	None

Appendix E: Forest Plots

E.1 Hip fracture patients versus controls



Appendix F:GRADE tables

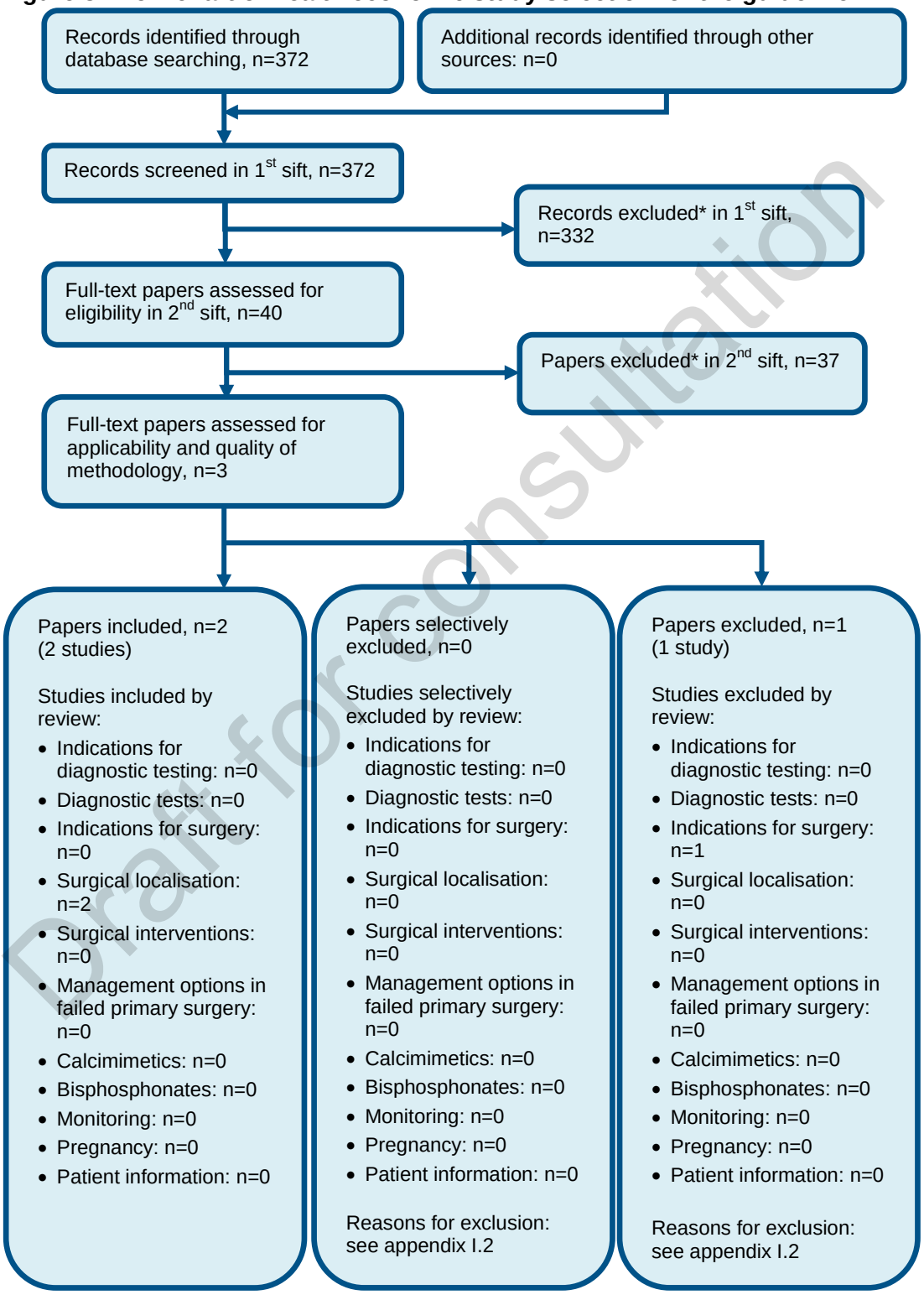
Table 13: Clinical evidence profile: Hip fracture patients versus controls

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hip fracture	Controls	Relative (95% CI)	Absolute		
diagnosis of PHPT												
1	Observational	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	21/444 (4.7%)	1.1%	RR 4.20 (1.60 to 11.04)	-	⊕⊕OO LOW	CRITICAL

[a] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.

Appendix G: Health economic evidence selection

Figure 3: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

No economic studies were included in this review.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 14: Studies excluded from the clinical review (diagnostic review)

Study	Exclusion reason
Akcay 2009[2]	Reference standard not reported
Al-Salem 1991[3]	Inappropriate study design – case series
Avioli 1987[5]	Article
Bhatti 2000[10]	No useable outcomes
Boughey 2004[13]	Inappropriate comparison. Study compared chloride phosphate ratio in patients with hypercalcaemia secondary to PHPT compared with that of healthy controls.
Bowman Jr 1972[14]	Case series
Christensson 1976[19]	Inappropriate population. Non-thiazide treated patients with hypercalcaemia detected in a health screening.
Cooper 1963[25]	Inappropriate study design – case series
Di Monaco 2004[30]	Study included in indications prognostic review
Ejlsmark-Svensson, 2018[34]	Incorrect study design – case control study
Fuss 1988[41]	Considered for inclusion in indications for testing prognostic review
Kim 2001[61]	No appropriate index tests
Mallmin 1991[66]	Full text paper not available
Mundy 1980[74]	No appropriate index tests
Ohe 2005[78]	No appropriate index tests
Pappu 2016[79]	Consider for inclusion in monitoring review
Press 2013[81]	No appropriate index tests. Study reports prevalence of PHPT from electronic medical record of a tertiary care centre.
St Goar1957[88]	Inappropriate study design – case series
Starup-Linde 2012[89]	No appropriate index tests
Younes 2003[103]	No appropriate index tests. Study examines the clinical presentation, indications for surgery, and outcomes of neck explorations for PHPT.
Wu 2016[100]	Literature review

Table 15: Studies excluded from the clinical review (prognostic review)

Study	Exclusion reason
Ahsan 2017[1]	n=25. Excluding studies less than 50 participants.
Anonymous 1974[4]	Inappropriate comparison. Vertebral crush fractures in surgically proved PHPT patients compared with patients with protrusive lumbar disc disease.
Benhamou 1991[6]	n=21. Excluding studies less than 50 participants.
Bhadada 2018[8]	Study considered for inclusion in monitoring review
Bhansali 2005[9]	Incorrect study design – case series
Bhatti 2000[10]	No comparison group
Bilezikian 2000[11]	Review comparing PHPT in USA and China

Study	Exclusion reason
Bolland 2008[12]	n=23. Excluding studies less than 50 participants.
Cassibba 2014[15]	Incorrect study design – retrospective analysis of a case series
Castellano 2017[16]	No useable outcomes
Chappard 2006[17]	Inappropriate variable. Study evaluates the bone status in various clinical forms of PHPT compared to healthy controls.
Chen 2010[18]	No appropriate variable. Study reports prevalence of PHPT in asymptomatic patients.
Chu 2010[20]	No appropriate variables. Study reports 25 years of experience in the management of renal bone disease.
Cipriani 2015[21]	Study considered for inclusion in monitoring review.
Clark 1991[22]	Full text paper not available
Conroy 2003[23]	Review – screened for relevant references
Cook 1945[24]	Narrative review on renal calculi associated with hyperparathyroidism
Corbetta 2005[26]	No appropriate variable. Study identifies clinical and biochemical background and risk factors for kidney stone development in PHPT.
De Geronimo 2006[27]	Study considered for inclusion in monitoring review.
Derrick 1982[29]	Article on renal calculi in PHPT
Diaz de la Guardia 2010[31]	Full text paper not available
Dimkovic 2002[32]	No appropriate variable. Study evaluated risk factors for stone formation in patients with raised iPTH and normal serum calcium.
Dolgin 1979[33]	No appropriate variable
Eller-Vainicher 2014[35]	Inappropriate variable. The study examined factors such as bone mineral density (BMD), calcium-sensing receptor (CASR) gene polymorphisms, associated with vertebral fracture risk in primary hyperparathyroidism.
Esho Sawa 1996[36]	n=15. Excluding studies less than 50 participants.
Eufrazino 2013[37]	Inappropriate study design – cross-sectional study
Evans 1984[38]	Inappropriate variable. Study reports metabolic studies in hypercalciuric and normocalciuric stone formers.
Foulds 1945[40]	Inappropriate study design – case report
Gallagher 1980[42]	n=35. Excluding studies less than 50 participants.
George 1965[43]	Inappropriate variables. Study measured the response to calcium infusion and phosphorous deprivation in patients with kidney stones.
Ghosh 1973[44]	Not appropriate study design
Gianotti 2006[45]	No appropriate variable. Study aimed to assess the differences in bone status in a series of consecutive patients affected by PHPT without overt renal failure at diagnosis.
Gopal 2010[46]	Inappropriate comparison. Study compared clinical presentation, biochemical, radiological features in adults with PHPT compared with that of children and adolescents with PHPT.
Gupta 1990[48]	Inappropriate study design – case series
Haddock 1983[49]	Case series – paper reports experience in the diagnosis and management of cases with PHPT
Harrison 1960[50]	Not appropriate study design – case series
Heath 1980[51]	Study considered for inclusion in monitoring review
Heilberg 2006[52]	Review – screened for relevant references
Herrera 2015[53]	Inappropriate study design. Cross-sectional study to assess the

Study	Exclusion reason
	prevalence of osteoporotic vertebral fractures in women over 45 years, based on the selection of a nationwide sample.
Holdaway 1982[54]	n=34. Excluding studies less than 50 participants.
Jha 2016[55]	Study considered for inclusion in monitoring review
Kelly 1972[56]	To be considered for inclusion in monitoring long term outcomes review
Kenny 1995[57]	Study considered for inclusion in monitoring review
Khosla 1999[59]	Study considered for inclusion in monitoring review
Khosla 2002[58]	Study considered for inclusion in monitoring review
Kobayashi 1997[62]	Study considered for inclusion in monitoring review
Kochersberger 1987[63]	Study considered for inclusion in monitoring review
Larsson 1989[64]	Study considered for inclusion in monitoring review
Larsson 1993[65]	Study considered for inclusion in monitoring review
Marchini 2018 [67]	Inappropriate variables. The study examined the impact of parathyroidectomy on the metabolic profile of patients with confirmed PHPT and urolithiasis.
McGeown 1960[68]	Not appropriate study design – case series
McIntosh 1958[69]	Not appropriate study design
Melton 1992[70]	Study considered for inclusion in monitoring review.
Miller 1952[71]	Inappropriate study design – case report
Mollerup 1999[72]	The aim of the study was to evaluate the risk of renal stone recurrence after successful surgical treatment of primary hyperparathyroidism
Mollerup 2002[73]	Inappropriate comparison. Study assed the risk of renal stones in patients with PHPT before and after surgery.
Nunziata 1991[77]	Case series
Pappu 2016[79]	No useable outcomes
Pentecost 1964[80]	Article on fractures
Rejnmark 2011[82]	Review. Screened for relevant references.
Sedlack 1990[83]	No useable outcomes
Selberherr 2017[84]	n=40. Excluding studies less than 50 participants.
Siilin 2011[86]	No appropriate variables. Study reports prevalence of PHPT in elderly men.
Silverberg 1990[87]	Inappropriate comparison – study compared patients with PHPT with and without nephrolithiasis with regard to biochemical profile and presence and extent of bone involvement
Starup-Linde 2012[89]	Incorrect study design – cross-sectional study
Sweetnam 1965[90]	Incorrect study design – case report
Vanderwalde 2009[91]	No appropriate variables. Study aimed to determine the influence of BMD together with parathyroidectomy on fracture risk in patients with PHPT.
Vestergaard 2000[92]	Inappropriate comparison. Study assessed the effects of surgery compared with conservative treatment (no surgery) for primary hyperparathyroidism.
Vestergaard 2003[93]	Inappropriate comparison. Study compared fracture risk before and after diagnosis in patients who had surgery with patients treated conservatively.
Vignali 2009[94]	Incorrect study design – case control study. The aim of the study was to evaluate the rate of vertebral fractures by dual-energy x-ray absorptiometry in postmenopausal women with sporadic PHPT and

Study	Exclusion reason
	compare the results with a control group.
Wilson 1988[97]	Study considered for inclusion in monitoring review
Wishart 1990[98]	Inappropriate variable. Study measured vertebral and forearm mineral density in post-menopausal women with mild PHPT and compared with expected values on the basis of age and years since menopause.
Yendt 1970[101]	Article on renal calculi
Yilmaz 2014[102]	Inappropriate variable. Study analysed changes in serum biochemical, PTH and mean platelet volume before and after parathyroid surgery.
Yu 2010[104]	Study included in monitoring review.

I.2 Excluded health economic studies

None.

Appendix J: Research recommendations

J.1 Primary hyperparathyroidism and neurocognitive function

Research question: What is the effect of primary hyperparathyroidism on neurocognitive function?

Why this is important:

A number of parameters of neurocognitive impairment have been reported in patients with primary hyperparathyroidism (PHPT), including fatigability, myalgia or bone pains, mood swings, abdominal pains/cramps, feeling weak, headaches, feeling irritable, memory problems and difficulty getting out of a car or chair [47] and many patients with PHPT describe a sense of "brain fog". In other conditions, hypercalcaemia has been reported to be an independent predictor of poor quality of life [99]. Although there have been some studies looking at psychological symptoms before and after surgery, the evidence base for case selection and the benefits of intervention (surgical or otherwise) generally focus on biomarkers such as the normalisation of serum adjusted calcium, PTH and bone mineral density.

Being able to provide evidence around the burden of neurocognitive impairments and the benefits of treatment on neurocognition would inform patients and clinicians alike in these outcomes.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Patients with a biochemical diagnosis of PHPT • pre-operative population (before and after surgery) • post-operative population • untreated population Intervention(s) and comparison(s): Incidence of neurocognitive symptoms Outcome(s) to include: • Symptoms • Memory (short-term, working and long-term) • Attention • Reasoning • Problem solving Covariate What is independent effect of serum calcium on outcome(s)?
Importance to patients or the population	Being able to provide evidence around the burden of neurocognitive impairments and benefits of treatment on neurocognition would inform patients and clinicians alike in these outcomes.
Relevance to NICE guidance	An understanding of the impact of PHPT and its treatment on neurocognitive function will provide an important outcome for future evaluations of PHPT as well as contributing to QALY models.
Relevance to the NHS	Neurocognitive impairment may require medical attention and psychiatric care or result in higher social dependency and have an impact on employment. The identification of the burden of such impairment in patients with PHPT and the potential to improve this aspect of their condition with targeted therapy may result in health and social cost savings.
National priorities	Improvements in mental health are amongst NHS England priorities for

	2018, (https://www.england.nhs.uk/wp-content/uploads/2017/03/NEXT-STEPS-ON-THE-NHS-FIVE-YEAR-FORWARD-VIEW.pdf). The avoidance of mental and psychological disorder associated with poorly evaluated or untreated PHPT should decrease the burden on currently overstretched services.
Current evidence base	No evidence was available for neurocognitive symptoms in the indications for diagnostic tests evidence review.
Equality	Those affected by neurocognitive impairment in the community in general are older and so there is a risk that their impairment is merely attributed to older age. However, the identification of those with PHPT and cognitive impairment who are most likely to benefit from intervention is an equitable goal.
Study design	Prospective cohort
Feasibility	People with severe neurocognitive impairment may not be able to participate (due to informed consent).
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

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