National Institute for Health and Care Excellence

Final

Hyperparathyroidism (primary): diagnosis, assessment and initial management

[D] Evidence review for surgical localisation

NICE guideline NG132

Diagnostic evidence review

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Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What is the clinical and cost effectiveness of using non-invasive imaging techniques (for example parathyroid ultrasound, sestamibi scanning, CT and MRI scanning) prior to surgery?

Review question: What is the clinical and cost effectiveness of using invasive imaging techniques (for example parathyroid venous sampling) prior to surgery?

Review question: What is the clinical and cost effectiveness of using intraoperative parathyroid hormone assays, methylene blue and intra operative frozen sections?

1.2 Introduction

This review focuses on the role of pre-operative imaging and intra-operative techniques to localise suspected abnormal parathyroid tissue. Without imaging, bilateral neck exploration is curative in approximately 95% of cases. However, pre-operative imaging is used to support the decision to perform a focused parathyroidectomy or to identify ectopic glands or multiglandular disease. Intraoperative monitoring may be used to verify the absence of other hypersecretory glands.

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 or over) with confirmed primary hyperparathyroidism caused by single adenoma, 4 gland hyperplasia, double adenoma or ectopic adenoma. Strata: • Previous parathyroidectomy • Pregnant women
Index test(s)	**Localisation techniques:** • US imaging using a high frequency probe, 10-15 MHz. • US imaging using a high frequency probe combined with colour Doppler ultrasound • Technetium 99m- Sestamibi scanning (planar) using single isotope dual phase scan (uses a single isotope and early and delayed phase imaging, usually at about 10-30 minutes and at 90-120 minutes) • Technetium 99m- Sestamibi scanning (planar) using dual isotope subtraction scan (uses isotope, 99 Tc sestamibi to image the parathyroids and either 123 Iodine or 99 Tc pertechnatate to image the thyroid, and then one set of images is subtracted from the other - often performed with early and delayed imaging) • Three-dimensional sestamibi scanning (also known as planar+ or SPECT)

	• SPECT-CT • MRI • 4DCT • CT • Parathyroid venous sampling • Methylene blue **Intra-operative techniques:** • Intra-operative frozen sections • Intra-operative parathyroid hormone (IOPTH) monitoring
Reference standard(s)	Histology and post-operative serum calcium level (for full details, see full review protocol).
Statistical measures [or] Outcomes	**For test-and-treat review:** • HRQOL • Mortality • Success (cure) / failure • Adverse events • BMD of the distal radius or the lumbar spine • Deterioration in renal function • Fractures (vertebral or long bone) • Length of hospital stay • Occurrence of kidney stones • Persistent hypercalcaemia • Reoperation • Unnecessary neck exploration **For diagnostic accuracy review:** Target condition (for localisation studies): correct localisation of adenoma (correctly localises the region/quadrant from which an abnormal gland is removed (rather than just correctly identifies hyperactive tissue anywhere, or correctly lateralises the hyperactive gland)). Target condition (for intra-operative tests): correct prediction of removal of all abnormal tissue. Outcomes of interest: Specificity Sensitivity

1.4 Clinical evidence

This review aimed to assess the clinical and cost effectiveness of various pre-operative and intra-operative tests to aid parathyroid surgery. These tests included both pre-operative/ intra-operative localisation techniques to aid localisation of the affected gland(s), and intra-operative techniques to determine when all affected tissue has been excised and aid the decision to terminate surgery. Evidence for both of these is presented separately in the review. The latter intra-operative tests included intra-operative parathyroid hormone monitoring (IOPTH) and intra-operative frozen sections. All other index tests in the protocol were localisation techniques. Additionally, for both categories evidence was sought from both test-and-treat RCT studies and from diagnostic accuracy studies. Therefore, the clinical evidence in this review was organised as follows:

- Imaging localisation tests – evidence from test-and-treat RCTs
- Imaging localisation tests – evidence from diagnostic accuracy studies

- Intra-operative tests (IOPTH and frozen section) – evidence from test-and-treat RCTs
- Intra-operative tests (IOPTH and frozen section) – evidence from diagnostic accuracy studies

1.4.1 Localisation and intra-operative techniques

1.4.1.1 Imaging localisation tests – diagnostic accuracy methods

The following adapted methods were used to assess the accuracy of the localisation index tests. Localisation index tests included ultrasound (US), sestamibi scanning (including planar, subtraction, SPECT or SPECT/CT), MRI, CT, 4D-CT, venous sampling and methylene blue. All of these index tests are used pre-operatively with the exception of methylene blue which is used intra-operatively. An adapted diagnostic accuracy method was used for this part of the review, as described below.

A standard diagnostic accuracy 2x2 table could not be used for this review, as there is more than 1 possible outcome for each person (unlike a standard diagnostic accuracy study where each person either has the disease or not). As each person has more than 1 parathyroid gland, there is more than 1 possible outcome for both the index test and the reference standard (i.e. imaging could predict 1 or more possible affected glands, and the final outcome could be a single adenoma, more than 1 adenoma, or hyperplasia).

Therefore, to overcome this problem, the following 2x2 table was devised at protocol stage for this review. This method was chosen as it allows the accuracy of the tests to be determined according to whether the imaging test would have predicted the correct surgical approach in each person (focused surgery or exploratory surgery). It was agreed that this approach would give the most relevant information for determining the most clinically effective localisation test.

		By the reference standard there was a single adenoma	
		YES	NO
Index test –		True positive (correct application of focused surgery) - imaging identifies a single adenoma location correctly	False positive (either focused surgery would fail or would convert to exploratory) - Imaging shows a single adenoma but there is actually a double adenoma - Imaging shows a single adenoma but there is actually hyperplasia - single on imaging but nothing found
		False Negative - nothing on imaging so single adenoma missed (do another imaging or exploratory surgery) - Imaging incorrectly identifies the location of a single adenoma (either surgery would fail or would convert to exploratory) - multiple findings on imaging but only a single located	True Negative (correct application of exploratory surgery) - Imaging shows nothing and there are no adenomas found - Imaging correctly identifies hyperplasia - Imaging correctly identifies double adenoma - Imaging shows nothing but there is actually a double - Imaging shows nothing but there is hyperplasia - Imaging shows multiple glands but not all in hyperplasia
	TOTAL	***Number of people with a single adenoma / should have focused***	***Number of people who should have exploratory surgery (either as no adenomas, hyperplasia or double adenomas).***

If a study provided enough evidence to categorise each included participant according to the above 2x2 table (both as to the localisation of affected tissue according to the index test and the final localisation outcome from the reference standard) then it was included. For example, if a study stated that a participant had an imaging scan suggesting a single adenoma but the final outcome determined by the histology and post-operative

normocalcaemia was a 4-gland hyperplasia, this person would be counted as a false positive. If it was not possible to categorise all the included participants for a given study into the above 2x2 table, then the study was excluded (for example, in people with persistent hypercalcaemia following surgery, unless the results of a further operation were provided in order to determine the final location according to the reference standard, then it would not be possible to determine whether the location of the affected tissue found on pre-operative imaging was correct or not).

The reference standard test must be the best available method to determine the actual location(s) of the affected tissue. It was agreed that the reference standard should include both histology and post-operative serum calcium levels. Histology alone was not sufficient as the reference standard, as although it can prove the presence of an adenoma, post-operative normocalcaemia is also required to prove that there was no further affected tissue remaining. Normocalcaemia in isolation is also not sufficient, unless the person was normocalcaemic after a single gland was removed. This is because, if more than 1 gland is removed, normocalcaemia could result if 1 or both of the glands were abnormal, and histology is required to determine if 1 or both were abnormal. Any studies not reporting both histology and post-operative normocalcaemia, in order to determine the actual location of abnormal tissue, were excluded.

By the above method, sensitivity and specificity would not have the same interpretation as in a standard diagnostic review. Sensitivity and specificity could be interpreted as follows:

- Sensitivity = % of people who have a single adenoma, who are correctly picked up by imaging tests (also the % of people who would get correctly applied focused surgery).
- Specificity = % of people who should get exploratory surgery (final diagnosis is >1 adenoma or hyperplasia), that do (imaging shows no adenoma, hyperplasia or double adenoma).

An index test with a low sensitivity (resulting from a high number of people in the bottom left cell) may mean that more people end up getting exploratory surgery who could have had focused surgery (if imaging shows more adenomas then there actually are), or it may mean that more people having failed surgery (if imaging shows the incorrect location of a single adenoma, although this may be picked up during the surgical procedure). An index test with a low specificity (resulting from a high number of people in the top right cell) may mean that more people would fail focused surgery and have persistent PHPT (as imaging would predict a single adenoma but they actually have >1).

Some diagnostic accuracy studies identified in the search provided accuracy data in different formats. These studies were only included in this review if it was possible to categorise all included participants in the study according to the above 2x2 table method. Some studies used a ‘per-gland’ method, assuming each person had 4 parathyroid glands and therefore determining 4 possible outcomes in the 2x2 table for each person. For example, if a person had 1 suspected adenoma located on imaging, and the reference standard confirmed a single adenoma at the same location, that person would have 1 true positive and 3 true negative results. Or, if a person had 1 suspected adenoma located on imaging but the final outcome according to the reference standard was 4-gland hyperplasia, then that person would be deemed to have 1 true positive and 3 false negative results. Another method adopted by some studies was an adapted ‘per-person’ method. If a person had all affected glands (either a single adenoma or more than 1 gland) correctly identified on imaging then they would be deemed a true positive. However, this causes problems of how to categorise people who have all their affected glands correctly identified on imaging, but the imaging also suggests further affected tissue in a location which is normal according to the reference standard. These people would be deemed to be true positives, even though relying on the imaging result alone would result in more glands being explored at surgery than was necessary.

Neither of the above methods ('per-gland' and 'per-person') were used for this review. The method used in this review was chosen as it allows the accuracy of the tests to be determined according to whether the imaging test would have predicted the correct surgical approach (focused surgery or exploratory surgery).

All clinical evidence was stratified according to whether the participants had undergone previous parathyroidectomy. Results were stratified into studies only including people having their first operation, studies only including people having re-operation, and studies with a mixed population of first operation or re-operation that could not be analysed separately. Data were available for the following tests for each population stratum:

- 1st operation (or studies including ≤5% people with re-operation)
  - US
  - MIBI
  - MIBI (subtraction)
  - SPECT
  - SPECT/CT
  - MRI
  - SPECT + US
- Mixed 1st operation and re-operation (>5% re-operation and not reported separately)
  - US
  - MIBI
  - MRI
  - CT
- Reoperation only
  - MIBI

For the localisation tests, sub selection of people based on the pre-operative imaging may introduce heterogeneity in the results, as studies using a pre-selection process will not be representative of the whole population. Therefore, sensitivity analysis was performed to stratify results into studies reporting all people (no pre-selection for the study based on imaging), studies only reporting people with a suspected single adenoma from imaging, and studies only reporting people with negative imaging. Results of this sensitivity analysis are reported in Table 13.

1.4.1.2 Intra-operative tests – diagnostic accuracy methods

The intra-operative tests of IOPTH and intra-operative frozen sections are not used to aid localisation of the affected tissue, but rather are used to determine whether all the affected tissue has been excised and whether surgery can be terminated. Therefore the method of assessing accuracy of these tests is different to the localisation tests.

The following 2x2 table was used to assess the accuracy of IOPTH and intra-operative frozen sections for predicting whether all abnormal tissue has been removed or not:

		Reference standard	
		+ve	-ve
Index test	+ve	True positive (>50% fall in PTH and all adenomas removed)	False positive (>50% fall in PTH but not all adenomas removed – person remains hypercalcaemic (up to 6 months) or requires re-op or subsequent glands resected in the same op)
	-ve	False Negative (no fall in PTH but all adenomas removed)	True Negative (no fall in PTH and not all adenomas removed – person remains hypercalcaemic (up to 6 months) or requires re-op or subsequent glands resected in the same op)
	TOTAL	***Reference standard positive***	***Reference standard negative***

Again, the reference standard was histology and post-operative serum calcium. Studies only stating the accuracy for prediction of post-operative normocalcaemia, without mention of histology, were excluded (unless all participants had normocalcaemia after removal of a single gland only). This is because, if >1 gland is removed, normocalcaemia is insufficient to determine whether 1 or both were abnormal. For example, IOPTH may not have fallen after removal of the first gland, so surgery continued and IOPTH fell after removal of the second gland. Without histology, it is not possible to classify the IOPTH result after removal of the first gland as a false negative or a true negative.

In this context:

- Sensitivity = the ability to identify people who have had all adenomas removed
- Specificity = the ability to identify people who have remaining abnormal tissue

An index test with a low sensitivity may result from a high proportion of people not having a drop in the IOPTH even when all abnormal tissue has been removed and therefore, may result in continuing to explore other glands unnecessarily if the decision to terminate surgery is based on the IOPTH alone. An index test with a low specificity may result from a high proportion of people having a drop in the IOPTH even though there is still abnormal tissue remaining and therefore, if the decision to terminate surgery is based on the IOPTH alone, the surgery would be terminated and the person would remain hypercalcaemic and require further surgery.

For IOPTH, it is possible to calculate the 2x2 table values in different ways for people who had >1 gland removed (i.e. for people with multigland disease). As there will be an IOPTH results after excision of the first gland (if this is negative in people who have remaining abnormal tissue and go on to have further glands excised, then people with MGD will be counted as true negatives) and an IOPTH result after excision of all abnormal glands (if this is positive in people with MGD once all their glands have been removed then people with MGD will be counted as true positives). In some studies, both methods can be calculated as they may report (in people with MGD) a negative IOPTH after excision of their first gland (a true negative due to remaining abnormal tissue), but a positive IOPTH after excision of all the abnormal glands (a true positive if all glands are removed and the person is rendered normocalcaemic). The preferred method for this review is to find the IOPTH accuracy after excision of a single gland or excision of the first gland (in people with MGD). This is because the predominant use of IOPTH is likely to be in focused surgery and the accuracy for predicting whether further abnormal tissue remains. Therefore, if it was possible to calculate both methods from a study, the result after excision of the first gland was preferred. The protocol stated a sensitivity analysis would be performed if there was heterogeneity to only include studies which give IOPTH results after excision of the first gland (or in studies where

all included participants had single gland disease). Results from the sensitivity analysis are reported in table 14.

There are various criteria for the IOPTH test to indicate a positive result. The criterion specified in this review was the Miami criteria (a drop in parathyroid hormone at 10 minutes post-excision of at least 50% of the highest baseline value (either pre-incision or pre-excision). However, studies were also included if they used a 50% drop in PTH from either baseline value. Studies using the criteria of a 50% drop ***and*** into the normal/reference range for PTH were excluded (unless a drop of 50% alone (regardless of whether it went into the normal range) could be calculated).

The protocol also specified PTH values taken at 5 or 20 minutes post-excision.

Studies were stratified according to the time point at which IOPTH was measured; studies reporting up to 10 minutes (sample taken at ≤10 minutes) and studies reporting at >10 minutes (7 studies analysed in this stratum: 4 studies[85, 94, 183, 537] took samples at 5, 10 and 15 minutes and the drop could be at any time point within 15 minutes, 1 study[207] only reported the median sample time of 13 minutes, 1 study[321] the sample was taken at 12 minutes and 1 study[314] the sample was taken at 20 minutes). Twenty-six studies were analysed in the stratum up to 10 minutes.

Some studies reported in a narrative in the results that some people had a delayed drop in IOPTH at 20 or 30 minutes. These studies did not specify in the methods that the 20-minute time point would be taken for all people without a drop in IOPTH at 10 minutes. Therefore it is unclear whether the 20-minute time point was assessed for everyone with an IOPTH negative at 10 minutes. Only the 10-minute time point was analysed for these studies[153, 224, 464, 504]. In addition, some studies reporting that some people had a delayed drop, the delayed drop was at 30 minutes[290, 291, 459] only the 10-minute data were analysed as 30 minutes is not included in the review protocol. Four studies actually reported in the methods that if the IOPTH did not fall at 10 minutes, a 20-minute sample would be taken before exploration continued[34, 69, 96, 486]. These studies have been analysed separately, as this is not the same criterion as everyone having the sample taken at 20 minutes. Three of these studies are also included in the up to 10 minute stratum as it was possible to calculate the results at 10 minutes only.

All clinical evidence was also stratified according to whether the participants had undergone previous parathyroidectomy. Results were stratified into studies only including people having their first operation, studies only including people having re-operation, and studies with a mixed population of first operation or re-operation that could not be analysed separately. For the IOPTH test, data were available for all time points for studies looking at first operation. For re-operation or mixed studies, only the ≤10 minute time point was available as summarised below:

- 1st operation (or studies including ≤5% people with re-operation)
    - >50% drop at ≤10 minutes
    - >50% drop at >10 minutes
    - >50% drop at 10 minutes (but in people without a drop at 10 minutes, a 20 minute time point sample was taken before continuing exploration).
- Mixed 1st operation and re-operation (>5% re-operation and not reported separately)
    - >50% drop at ≤10 minutes
      Data not available for any other time points
- Reoperation only
    - >50% drop at ≤10 minutes (data only available from a study subgroup analyses)
      Data not available for any other time points

The protocol stated a sensitivity analysis would be performed if there was heterogeneity to only include studies which give IOPTH results after excision of the first gland (or in studies

where all included participants had single gland disease). Results of this sensitivity analysis are reported in Table 13.

1.4.2 Included studies

Fifty six studies were included in the clinical evidence review, (Aarum 2007[1], Agarwal 2012[4], Agha 2007[7], Barczynski 2007[34], Bobanga 2017[55], Bonjer 1997[57], Bradley 2016[60], Calo 2013[69], Casas 1994[79], Cayo 2009[85], Chen 2005[94], Chick 2017[96], Garner 1999[153], Hamilton 1988[181], Hanif 2006[183], Harris 2008[186], Hathaway 2013[189], Hindie 1998[197], Hughes 2011[207], Hwang 2010[209], Iacobone 2005[210], Jaskowiak 2002[224], Kairaluoma 1994[234], Kim 2015[250], Krausz 2006[264], Kumar 2000[268], Lee 2014[276], Lo 2003[290], Lo 2007[291], Lombardi 2008[292], Michel 2013[314], Miccoli 2008[313] Miura 2002[317], Morks 2001[321], Mozzon 2004[325], Nilsen 2006[343], Nordin 2001[347], Orloff 2001 [355], Ozkul 2015[358], Patel 1998[365], Richards 2011[391], Rossi 2000[397], Rubello 2006[401], Saaristo 2002[409], Sagan 2010[412], Sprouse 2001[457],Stalberg 2006 [459], Stenner 2009[464], Tampi 2014[476], Timm 2004[486], van Ginhoven 2011[502],Vignali 2002[504], Wade 2012[508],Wei 1997[515],Witteveen 2011[524], Ypsilantis 2010[537])

Three studies were RCT test-and-treat studies assessing the use of pre-operative imaging (2 studies) or IOPTH (1 study). Fifty-three studies assessed the accuracy of pre-operative imaging or intra-operative tests. All the included studies are summarised in table 2 and table 3 below.

1.4.3 Excluded studies

See the excluded studies list in appendix J.

1.4.4 Summary of clinical studies included in the evidence review

Table 2: Summary of test-and-treat studies included in the evidence review

Study	Population	Index test	Comparison	Outcomes
Aarum 2007[1]	n=100 1st surgery (reported)	MIBI + US	Randomised to localisation or no localisation, and treated accordingly – i.e. if single detected on imaging then had MIP, otherwise had bilateral (all control group had bilateral)	Normocalcaemia Adverse events (transient recurrent nerve paralysis)
Kairaluoma 1994[234]	n=28 1st surgery (reported)	US	Group 1: results of US reported to surgeon beforehand, group 2: results not reported to surgeon. All people had bilateral surgery, in group 1 surgery was started on side indicated by US, in group 2 started on LHS	Normocalcaemia Length of hospital stay
Miccoli 2008[313]	N=40 Analysed in 1st surgery (not reported) only included patients positive for a single adenoma on pre-operative localisation with US and MIBI	IOPTH	Randomised to IOPTH or no IOPTH to see when the surgery should be terminated – group 1 terminated if drop in IOPTH, group 2 had 4 gland visualisation	Normocalcaemia Adverse events

Table 3: Summary of diagnostic accuracy studies included in the evidence review

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
Agarwal 2012[4]	n=59 Analysed in 1st surgery (not reported) Only included people with solitary adenoma (retrospective inclusion from histology)	IOPTH	IOPTH results after 1st gland excised(all had solitary adenoma)	• >50% at 10 minutes compared to pre-excision
Agha 2007[7]	n=58 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after all glands excised	• >50% drop at 10 minutes compared to baseline (start of anaesthesia)

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
Barczynski 2007[34]	n=177 (n=115 with IOPTH) 1st surgery (reported) Only included people with suggested single adenoma by at least one imaging (MIBI or US).	IOPTH	IOPTH results after 1st gland excised	• Miami (≥50% drop at 10 minutes compared to the highest baseline • ≥50% drop at 10 minutes compared to the highest baseline (if this didn't occur within 10 minutes, a drop of >50% within 20 min)
Bobanga 2017[55]	n=127 Analysed in 1st surgery (not reported) Only included people with concordant imaging SPECT and US predicting a single adenoma	SPECT and US (concordant)	n/a	n/a
Bonjer 1997[57]	n=27 (n=25 with PHPT) 16% re-operation (results reported separately for 1st operation and re-operation)	MIBI	n/a	n/a
Bradley 2016[60]	n=49 Analysed in 1st surgery (not reported) Only included people with negative sestamibi scan and US suggesting a single adenoma	US	n/a	n/a
Calo 2013[69]	n=188 Analysed in 1st surgery (not reported) Only included people undergoing focused PTx	IOPTH	IOPTH results after 1st gland excised	• Irvin (>50% drop at 10 minutes from the highest baseline (if this didn't occur within 10 minutes, a drop of >50% within 20 min and/or a residual PTH-20 min level within the reference range)
Casas 1994[79]	N=42 (n=21 with MIBI) Analysed in 1st surgery (not reported)	MIBI (subtraction)	n/a	n/a
Cayo 2009[85]	n=161 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after all glands excised	• >50% drop at 5, 10 or 15 minutes compared to pre-incision

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
	Only included people with MGD on pathology			
Chen 2005[94]	n=345 (n=188 IOPTH) Analysed in 1st surgery (not reported) Only included people with positive localisation studies for a single adenoma and candidates for MIP.	IOPTH	IOPTH results after 1st gland excised	• >50% at 5, 10 or 15 minutes compared to pre-incision
Chick 2017[96]	n=157 (n=79 IOPTH) Analysed in 1st surgery (not reported) Only included people eligible for MIP (at least one localisation study suggesting solitary adenoma)	IOPTH	IOPTH results after all glands excised	• Miami (≥50% drop at 10 minutes compared to the highest baseline • ≥50% drop at 10 minutes compared to the highest baseline (if this didn't occur within 10 minutes, a drop of >50% within 20 min)
Garner 1999[153]	n=130 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after all glands excised	• >50% drop at around 10 minutes (although one person had a delayed drop of 24 minutes)[(a)].
Hamilton 1988[181]	n=10 1st surgery (reported)	MRI	n/a	n/a
Hanif 2006[183]	n=51 5.9% re-operation (analyse in 1st operation stratum as ≤5% re-operation)	IOPTH	IOPTH results after all glands excised	• ≥50% at 5, 10 or 15 minutes relative to the preoperative value
Harris 2008[186]	n=23 Analysed in 1st surgery (not reported)	SPECT/CT	n/a	n/a
Hathaway 2013[189]	n=303 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after 1st gland excised (all had solitary adenoma)	• >50% drop at 5 or 10 minutes from the highest baseline

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
	Only included people with single gland disease, people with more than one gland excised were excluded			
Hindie 1998[197]	n=30 1st surgery (reported)	MIBI MIBI (subtraction)	n/a	n/a
Hughes 2011[207]	n=228 1st surgery (reported) Only included people with multigland disease from histology	IOPTH	IOPTH results after all glands excised	• ≥50% drop at a median of 13 minutes (5-35 minutes) from highest baseline
Hwang 2010[209]	n=280 1st surgery (reported) Subselection of people selected for MIP. Excluded people whose surgery was begun as open procedure	IOPTH	IOPTH results after 1st gland excised	• Miami criteria - >50% drop at 10 minutes from highest pre-excision value a
Iacobone 2005[210]	n=102 1st surgery (reported)	IOPTH Frozen Section	IOPTH results after 1st gland excised	• >50% drop at 5 or 10 minutes from pre-incision
Jaskowiak 2002[224]	n=57 12% previous re-operation (not reported separately, analysed in mixed 1st and re-operation stratum)	IOPTH MIBI US	IOPTH results after 1st gland excised	• >50% drop at 10 minutes from the highest baseline value (other criteria reported in study but this can be calculated)[(a)]
Kim 2015[250]	n=53 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after all glands excised	• >50% at 10 minutes compared to before resection
Krausz 2006[264]	n=36 16.7% previous re-operation (not reported separately, analysed in mixed 1st and re-operation)	MIBI (note: some people may have had MIBI subtraction)	n/a	n/a

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
Kumar 2000[268]	n=30 Analysed in 1st surgery (not reported)	MIBI (subtraction)	n/a	n/a
Lee 2014[276]	n=557 (n=547 IOPTH) 1st surgery (reported) Intended initial operation was a MIP (excluded people when the disease could not be located using pre-operative imaging)	IOPTH	Unclear	• ≥50% drop at 10 minutes compared to the pre-incision value
Lo 2003[290]	n=66 1st surgery (reported) Only included those suspected of having a single adenoma on imaging and underwent endoscopic assisted surgery	IOPTH	IOPTH results after 1st gland excised (all had solitary adenoma)	• >50% drop at 10 minutes compared to the pre-incision value[(a)]
Lo 2007[291]	n=100 1st surgery (reported) Only included those suspected of having a single adenoma on imaging and underwent MIP	IOPTH	IOPTH results after 1st gland excised	• >50% drop at 10 minutes compared to the baseline value[(a)]
Lombardi 2008[292]	n=207 Analysed in 1st surgery (not reported) Selected for focused surgery, suspected single adenoma (by concordant results of US and MIBI)	IOPTH	IOPTH results after 1st gland excised	• Miami (≥50% drop at 10 minutes compared to the highest baseline)
Michel 2013[314]	n=58 1st surgery (reported)	IOPTH	IOPTH results after 1st gland excised (all had solitary adenoma)	• >50% drop and within the normal range at 20 minutes (as all people were IOPTH positive, we can calculate that all fit the review protocol criteria of >50% drop (regardless of whether in the reference range or not).

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
Miura 2002[317]	n=115 7.8% previous re-operation (analysed in mixed 1st and re-operation)	IOPTH	Unclear	• >50% drop at 10 minutes compared to the pre-incision value
Morks 2001[321]	n=65 1st surgery (reported)	IOPTH	IOPTH results after 1st gland excised	• >50% drop at 12 minutes compared to the pre-incision value
Mozzon 2004[325]	n=268 (n=263 IOPTH analysis) 2.6% re-operation (analyse in 1st operation stratum as ≤5% re-operation)	IOPTH	IOPTH results after all glands excised	• >50% drop at 10 minutes from highest baseline
Nilsen 2006[343]	n=100 1st surgery (reported)	IOPTH MIBI	IOPTH results after 1st gland excised	• >50% drop at 5 or 10 minutes from pre-incision
Nordin 2001[347]	n=33 1st surgery (reported)	SPECT	n/a	n/a
Orloff 2001[355]	n=23 Analysed in 1st surgery (not reported)	MIBI	n/a	n/a
Ozkul 2015[358]	n=11 1st surgery (reported)	SPECT	n/a	n/a
Patel 1998[365]	n=33 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after 1st gland excised (all had solitary adenoma)	• >50% drop at 7 minutes from pre-excision
Richards 2011[391]	n=1882 1st surgery (reported)	IOPTH	IOPTH results after all glands excised	• ≥50% drop at 10 minutes from baseline (either pre-incision or pre-excision)
Rossi 2000[397]	n=11 73% re-operation (analysed in mixed 1st and re-	IOPTH MIBI	IOPTH results after 1st gland excised (all had	• >50%drop at 5 or 10 minutes from baseline (unclear if pre-incision or pre-

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
	operation; except for IOPTH can subgroup into 1st op and re-op)	US MRI CT	solitary adenoma)	excision)
Rubello 2006[401]	n=54 (n=22 analysed) 1st surgery (reported) Only included people with evidence of a solitary adenoma on MIBI	IOPTH SPECT	IOPTH results after all glands excised	• ≥50% drop at 10 minutes from pre-excision
Saaristo 2002[409]	n=20 1st surgery (reported)	MIBI	n/a	n/a
Sagan 2010[412]	n=33 1st surgery (reported)	IOPTH	IOPTH results after 1st gland excised	• >50% drop at10 minutes from pre-incision
Sprouse 2001[457]	n=56 1st surgery (reported) Excluded people with negative MIBI or suspicion of multigland disease (only included people with positive MIBI suggesting single gland disease)	MIBI (note: some people may have had MIBI subtraction)	n/a	n/a
Stalberg 2006 [459]	n=100 1st surgery (reported) Subselection of people with suspected single gland disease from MIBI results (people with negative MIBI and MIBI suggesting multiple sites excluded)	IOPTH	IOPTH results after 1st gland excised	• >50% drop at10 minutes from highest pre-incision or pre-excision[(a)]
Stenner 2009[464]	n=12 1st surgery (reported) Subselection of people with single adenoma	IOPTH	IOPTH results after 1st gland excised (all had solitary adenoma)	• >50% drop at10 minutes from pre-incision [(a)]

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
	<35mm on pre-operative imaging.			
Tampi 2014[476]	n=7 Analysed in 1st surgery (not reported)	IOPTH Frozen section	IOPTH results after 1st gland excised (all had solitary adenoma)	• >50%drop at 10 minutes from baseline (unclear if pre-incision or pre-excision)
Timm 2004[486]	n=40 (n=35 IOPTH) Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after 1st gland excised	• >50% drop at 10 minutes from pre-operative or pre-excision levels • >50% drop at 10 minutes from pre-operative or pre-excision levels (if there was no drop at 10 minutes, samples were taken at 15 and 20 minutes)
van Ginhoven 2011[502]	n=46 8.7% re-operation (not reported separately, analysed in mixed 1st and re-operation)	US (note: when a possible enlargement was identified, colour Doppler US was used to determine the vascularity of the lesion) Some people will have had colour Doppler US (unclear if everyone would have received this; negative	n/a	n/a

Study	Population (number participants; 1st/re-op strata; any preselection)	Index test(s)	IOPTH results after 1st gland / all glands excised	IOPTH threshold & timepoint
		scans would not have used Doppler), therefore analysed with other studies assessing US alone		
Vignali 2002[504]	n=206 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after 1st gland excised	• >50% drop at 10 minutes from the highest pre-excision or pre-incision value[(a)]
Wade 2012[508]	n=58 1st surgery (reported)	IOPTH	IOPTH results after all glands excised	• ≥50% drop at 10 minutes from the highest baseline (either pre-incision or at time of parathyroid removal, time zero)
Wei 1997[515]	n=22 1st surgery (reported)	MIBI	n/a	n/a
Witteveen 2011[524]	n=42 (only n=23 1st surgery group analysed) 1st surgery (reported) Subselection of people with single gland disease	SPECT	n/a	n/a
Ypsilantis 2010[537]	n=11 Analysed in 1st surgery (not reported)	IOPTH	IOPTH results after 1st gland excised	• ≥50% drop within 15 minutes (at 5, 10 or 15 minutes) from baseline (immediately after excision, time zero)

(a) Some studies reported in a narrative in the results that some people had a delayed drop in IOPTH at 20 or 30 minutes. These studies did not specify in the methods that the 20 minute timepoint would be taken for all people without a drop in IOPTH at 10 minutes. Therefore it is unclear whether the 20 min timepoint was assessed for everyone with an IOPTH negative at 10 minutes. In addition, the 30 minute timepoint is not included in the review protocol. Only the 10 minute timepoint was analysed for these studies.

See appendix D for full evidence tables.

1.4.5 Clinical Evidence Summaries

1.4.5.1 Imaging localisation tests – test and treat studies

Table 4: Clinical evidence summary (first operation stratum): MIBI+US pre-operative localisation versus no pre-operative localisation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Pre-op MIBI and US versus no pre-op localisation (95% CI)
Normocalcaemia	99 (1 study) 6 months	MODERATE[a] due to risk of bias	RR 1.02 (0.93 to 1.12)	Moderate	
				940 per 1000	19 more per 1000 (from 66 fewer to 113 more)
Adverse events transient recurrent nerve paralysis	99 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.54 (0.15 to 380.14)	Moderate	
				0 per 1000	20 more per 1000 (from 30 fewer to 70 more)

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.
b Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs

Table 5: Clinical evidence summary (first operation stratum): US pre-operative localisation versus no pre-operative localisation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No pre-op US	Risk difference with Pre-op US (95% CI)
Cure No missed glands and normocalcaemia[a]	28 (1 study) 1 years	VERY LOW[b,c] due to risk of bias, imprecision	RR 1.16 (0.91 to 1.48)	Moderate	
				857 per 1000	137 more per 1000 (from 77 fewer to 411 more)
Length of hospital stay (days)	28 (1 study)	VERY LOW[b,c] due to risk of		The mean length of hospital stay (days) in the control groups was	The mean length of hospital stay (days) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No pre-op US	Risk difference with Pre-op US (95% CI)
	1 years	bias, imprecision		5.8 days	0.4 higher (1.23 lower to 2.03 higher)

a Study notes that glands could not have been located using US in the 2 people not cured in the control group
b 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.
c Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs

1.4.5.2 Imaging localisation tests – diagnostic accuracy studies

Table 6: Clinical evidence summary: 1st operation stratum

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
Ultrasound					
US	1	49	VERY LOW[a,c,d] due to risk of bias, imprecision, indirectness	87% (74% to 95%)	0% (0% to 84%)
MIBI					
MIBI	7	274	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	Range 78% - 98%[f]	Range 0% - 100%[f]
MIBI (subtraction)					
MIBI (subtraction)	3	81	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	Range 88% - 100%[f]	Range 0% - 100%[f]
MIBI (SPECT)					
MIBI (SPECT)	4	88	VERY LOW[b,c,d] due to inconsistency,	Range 61% - 100%[g]	Range 92% - 100% (2 studies not estimable)[g]

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
			indirectness, imprecision		
MIBI (SPECT/CT)					
MIBI (SPECT/CT)	1	23	VERY LOW[a,d] due to risk of bias, imprecision	89% (65% to 99%)	60% (15% to 95%)
MRI					
MRI	1	10	LOW[a,d] due to risk of bias, imprecision	90% (55% to 100%)	Not estimable
CT					
CT	0	-	-	-	-
SPECT + US					
SPECT + US	1	127	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	98% (94% to 100%)	0% (0% to 52%)

The committee deemed the sensitivity and specificity as equally important for decision-making. The assessment of the evidence quality was conducted with equal emphasis on both the sensitivity and specificity (if there was no inconsistency or imprecision in either measure then no downgrade was made, but if there was inconsistency or imprecision in either the sensitivity or specificity then appropriate downgrades were made for inconsistency/imprecision).

(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) Inconsistency was assessed by inspection of the sensitivity and specificity plots. The evidence was downgraded by 1 increment if the individual study point estimates varied across 2 areas: both above and below 50%, or both above and below an acceptable threshold set at 90% (for example, values fall in both 0–50% and 50–90%, or in both 50–90% and 90–100%). The evidence was downgraded by 2 increments if the individual study values varied across 3 areas (for example, values fall in all 3 areas of 0–50%, 50–90% and 90–100%).

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(d) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed 1 clinical decision threshold: 50% or 90%. The evidence was downgraded by 2 increments when the confidence interval around the point estimate crossed 2 clinical decision thresholds (50% and 90%).

(e) Pooled sensitivity/specificity from diagnostic meta-analysis

(f) Unable to meta-analyse due to heterogeneity

(g) Meta-analysis not performed as 'specificity' not estimable for 2 studies and unable to perform meta-analysis with only the 2 remaining studies

Table 7: Clinical evidence summary: Mixed 1st and re-operation stratum

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
Ultrasound					
US	3	114	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	Range 64% - 86%[e]	Range 33% - 71% (1 study not estimable)[e]
MIBI					
MIBI	3	104	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	Range 64% - 97%[f]	Range 57%-100% (1 study not estimable)[f]
MIBI (subtraction)					
MIBI (subtraction)	0	-	-	-	-
MIBI (SPECT)					
MIBI (SPECT)	0	-	-	-	-
MIBI (SPECT/CT)					
MIBI (SPECT/CT)	0	-	-	-	-
MRI					
MRI	1	4	VERY LOW[a,d] due to risk of bias, imprecision	50% (7% to 93%)	Not estimable
CT					
CT	1	3	VERY LOW[a,d] due to risk of bias,	33% (1% to 91%)	Not estimable

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
			imprecision		
SPECT + US					
MIBI (SPECT/CT)	0	-	-	-	-

The committee deemed the sensitivity and specificity as equally important for decision-making. The assessment of the evidence quality was conducted with equal emphasis on both the sensitivity and specificity (if there was no inconsistency or imprecision in either measure then no downgrade was made, but if there was inconsistency or imprecision in either the sensitivity or specificity then appropriate downgrades were made for inconsistency/imprecision).

(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) Inconsistency was assessed by inspection of the sensitivity and specificity plots. The evidence was downgraded by 1 increment if the individual study point estimates varied across 2 areas: both above and below 50%, or both above and below an acceptable threshold set at 90% (for example, values fall in both 0–50% and 50–90%, or in both 50–90% and 90–100%). The evidence was downgraded by 2 increments if the individual study values varied across 3 areas (for example, values fall in all 3 areas of 0–50%, 50–90% and 90–100%).

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(d) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed 1 clinical decision threshold: 50% or 90%. The evidence was downgraded by 2 increments when the confidence interval around the point estimate crossed 2 clinical decision thresholds (50% and 90%).

(e) Meta-analysis not performed as 'specificity' not estimable for 1 study and unable to perform meta-analysis with only the 2 remaining studies

(f) Meta-analysis not performed as 'specificity' not estimable for 1 study and unable to perform meta-analysis with only the 2 remaining studies

Table 8: Clinical evidence summary: Re-operation stratum

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
MIBI					
MIBI	1	4	LOW[a]	100% (40% to 100%)	Not estimable

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
			due to imprecision		

The committee deemed the sensitivity and specificity as equally important for decision-making. The assessment of the evidence quality was conducted with equal emphasis on both the sensitivity and specificity (if there was no inconsistency or imprecision in either measure then no downgrade was made, but if there was inconsistency or imprecision in either the sensitivity or specificity then appropriate downgrades were made for inconsistency/imprecision).
(a)Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed 1 clinical decision threshold: 50% or 90%. The evidence was downgraded by 2 increments when the confidence interval around the point estimate crossed 2 clinical decision thresholds (50% and 90%).

1.4.5.3 Intra-operative tests – test and treat studies

Table 9: Clinical evidence summary (first operation stratum): IOPTH versus no IOPTH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No IOPTH (to determine termination of surgery)	Risk difference with IOPTH (95% CI)
Normocalcaemia (6 months)	40 (1 study) 6 months	MODERATE[a] due to risk of bias	RR 0.95 (0.83 to 1.09)	Moderate	
				1000 per 1000	50 fewer per 1000 (from 170 fewer to 90 more)
Post-operative complications	40 (1 study) 6 months	VERY LOW [a,c] due to risk of bias, imprecision	Not estimable	Moderate	
				0 per 1000	0 fewer per 1000 (from 90 fewer to 90 more)[b]

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.
b No events in either arm
c Downgraded by 1 increment if there was serious imprecision (sample size >70<350), and downgraded by 2 increments if there was very serious imprecision (sample size <70).

1.4.5.4 Intra-operative tests – diagnostic accuracy studies

Table 10: Clinical evidence summary: 1st operation stratum

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
IOPTH					
>50% drop at ≤10 minutes	26	4726	VERY LOW[b,d] due to inconsistency, imprecision	Pooled[e,f] 97.1 (95.5 to 98.5)%	Pooled[e,f] 86.8% (73.7 to 96.7)%
>50% drop at >10 minutes	7	762	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	Range 94% - 100%[g]	Range 50% - 100% (2 studies not estimable)[g]
>50% drop at 10 minutes, plus 20 minute sample in people without a drop at 10 minutes	4	417	LOW[a,d] due to risk of bias, imprecision	Range 97% - 100%[g]	Range 93% - 100%[g]
Frozen Section					
Frozen Section	2	108	MODERATE[d] due to imprecision	94% [h] 100%	22% [h] Not estimable

The committee deemed the sensitivity and specificity as equally important for decision-making. The assessment of the evidence quality was conducted with equal emphasis on both the sensitivity and specificity (if there was no inconsistency or imprecision in either measure then no downgrade was made, but if there was inconsistency or imprecision in either the sensitivity or specificity then appropriate downgrades were made for inconsistency/imprecision).

(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) Inconsistency was assessed by inspection of the sensitivity and specificity plots. The evidence was downgraded by 1 increment if the individual study point estimates varied across 2 areas: both above and below 50%, or both above and below an acceptable threshold set at 90% (for example, values fall in both 0–50% and 50–90%, or in both 50–90% and 90–100%). The evidence was downgraded by 2 increments if the individual study values varied across 3 areas (for example, values fall in all 3 areas of 0–50%, 50–90% and 90–100%).

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect

(d) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the

point estimate crossed 1 clinical decision threshold: 50% or 90%. The evidence was downgraded by 2 increments when the confidence interval around the point estimate crossed 2 clinical decision thresholds (50% and 90%).

(e) Pooled sensitivity/specificity from diagnostic meta-analysis

(f) For 7 of the 26 studies, specificity is not estimable and therefore unable to include in the meta-analysis. The meta-analysis was run twice (sensitivity analysis to check imputed values). Firstly for all 26 studies, with a value of 1 inserted in the TN cell for any studies with zero TNs. Secondly with these 7 studies excluded, only 19 studies included in the meta-analysis (for which specificity was estimable).The pooled sensitivity value was the same in both models. The specificity was 88.9% if all 26 studies were included and 86.8% if only the 19 studies with an estimable specificity were included (around a 2% over prediction of specificity by imputing values for TNs). Pooled specificity result presented here is for 19 included studies (7 studies with specificity not estimable excluded) as this is likely to give the best estimate of specificity.

(g) Unable to meta-analyse, either with all 7 studies included (and TN values imputed for the studies where specificity was not estimable), or with only the 5 studies where specificity was estimable.

(h) Unable to meta-analyse

Table 11: Clinical evidence summary: Mixed 1st and re-operation stratum

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
IOPTH					
>50% drop at ≤10 minutes	2	172	VERY LOW[a,b] due to inconsistency, imprecision	92% 82%	75% 0%
>50% drop at >10 minutes	0	-	-	-	-
>50% drop at 10 minutes, plus 20 minute sample in people without a drop at 10 minutes	0	-	-	-	-
Frozen Section					
Frozen section	0	-	-	-	-

The committee deemed the sensitivity and specificity as equally important for decision-making. The assessment of the evidence quality was conducted with equal emphasis on both the sensitivity and specificity (if there was no inconsistency or imprecision in either measure then no downgrade was made, but if there was inconsistency or imprecision in either the sensitivity or specificity then appropriate downgrades were made for inconsistency/imprecision).

(a) Inconsistency was assessed by inspection of the sensitivity and specificity plots. The evidence was downgraded by 1 increment if the individual study point estimates varied across 2 areas: both above and below 50%, or both above and below an acceptable threshold set at 90% (for example, values fall in both 0–50% and 50–90%, or in both 50–90% and 90–100%). The evidence was downgraded by 2 increments if the individual study values varied across 3 areas (for example, values fall in all 3 areas of 0–50%, 50–90% and 90–100%).

(b) Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed 1 clinical decision threshold: 50% or 90%. The evidence was downgraded by 2 increments when the confidence interval around the point estimate crossed 2 clinical decision thresholds (50% and 90%).

Table 12: Clinical evidence summary: Re-operation stratum

Index Test (Threshold)	Number of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)
IOPTH					
>50% drop at ≤10 minutes	1	3	VERY LOW[a,b] due to risk of bias, imprecision	100% (29% to 100%)	Not estimable
>50% drop at >10 minutes	0	-	-	-	-
>50% drop at 10 minutes, plus 20 minute sample in people without a drop at 10 minutes	0	-	-	-	-
Frozen Section					
Frozen section	0	-	-	-	-

The committee deemed the sensitivity and specificity as equally important for decision-making. The assessment of the evidence quality was conducted with equal emphasis on both the sensitivity and specificity (if there was no inconsistency or imprecision in either measure then no downgrade was made, but if there was inconsistency or imprecision in either the sensitivity or specificity then appropriate downgrades were made for inconsistency/imprecision).

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. Imprecision was assessed based on inspection of the confidence region in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed 1 clinical decision threshold: 50% or 90%. The evidence was downgraded by 2 increments when the confidence interval around the point estimate crossed 2 clinical decision thresholds (50% and 90%).

Table 13: Summary of sensitivity analyses for Imaging results

Sensitivity analysis (if heterogeneity) to subgroup into only those studies recruiting people with a single positive adenoma on imaging, those studies recruiting people with negative imaging and those studies recruiting all people regardless of imaging result.

Analysis	Heterogeneity observed?	Sensitivity analysis performed?	Sensitivity analysis resolved heterogeneity?	Results reported

Analysis	Heterogeneity observed?	Sensitivity analysis performed?	Sensitivity analysis resolved heterogeneity?	Results reported
First surgery stratum				
US	No	No	-	Overall
MIBI	Yes	Yes	No	Overall (sensitivity analysis not presented as heterogeneity not resolved)
MIBI (subtraction)	Yes	Yes	No	Overall
MIBI (SPECT)	Yes	Yes	No	Overall (sensitivity analysis not presented as heterogeneity not resolved)
MIBI (SPECT/CT)	No	No	-	Overall
MRI	No	No	-	Overall
SPECT + US	No	No	-	Overall
Mixed (1st surgery and re-operation) stratum				
US	Yes	Yes	No	Overall (sensitivity analysis not presented as heterogeneity not resolved)
MIBI	Yes	Yes	No	Overall (sensitivity analysis not presented as heterogeneity not resolved)
MRI	No	No	-	Overall
CT	No	No	-	Overall
Re-operation stratum				
MIBI	No	No	-	-

Table 14: Summary of sensitivity analyses for IOPTH results

Sensitivity analysis (if heterogeneity) to subgroup into those studies reporting IOPTH results after excision of the first gland only.

Stratum	Heterogeneity observed?	Sensitivity analysis performed?	Sensitivity analysis resolved heterogeneity?	Results reported
1st operation (>50% drop at ≤10 minutes)	Yes	Yes (to only include studies with IOPTH result after excision of 1st gland)	No	Overall (sensitivity analysis not presented as heterogeneity not resolved)

Stratum	Heterogeneity observed?	Sensitivity analysis performed?	Sensitivity analysis resolved heterogeneity?	Results reported
1st operation (>50% drop at >10 minutes)	Yes	Yes (to only include studies with IOPTH result after excision of 1st gland)	No	Overall (sensitivity analysis not presented as heterogeneity not resolved)
1st operation (>50% drop at 10 minutes, plus 20 minute sample in people without a drop at 10 minutes)	No	No	-	Overall
Mixed 1st and re-operation (>50% drop at ≤10 minutes)	Yes	No (only 2 studies available)	-	Overall
Re-operation (>50% drop at ≤10 minutes)	No	No	-	Overall

1.5 Economic evidence

1.5.1 Included studies

Two health economic studies were identified with the relevant comparison and have been included in this review.[29, 363] These are summarised in the health economic evidence profiles below (Table 15 and Table 16) and the health economic evidence tables in appendix H.

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.

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

1.5.3 Summary of studies included in the economic evidence review

Table 15: Health economic evidence profile: Non-invasive imaging

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Pata et al 2011 [363] [Italy]	Partially applicable	Potentially serious limitations	• Within-cohort study analysis (same paper) • Comparative costing • Population: People diagnosed with PHPT who underwent parathyroidectomy • Comparators: 1. SPECT 2. SPECT/CT • Follow-up: 6 months	2-1: cost saving £91[(c)]	n/a	n/a	No sensitivity analysis conducted.

Abbreviations: CT: computerised tomography; SPECT: Single-photon emission computed tomography.
(a) Italian resource use (2004-2009) and unit costs (2009) data may not reflect current NHS context. QALYs not used as outcome measure.
(b) Analysis is based on a cohort study. Within-study analysis and so does not reflect full body of evidence. No exploration of uncertainty.
(c) 2009 Euros converted to 2009 UK pounds[354]

Table 16: Health economic evidence profile: Intra-operative techniques

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Badii et al 2016 [Italy] [29]	Partially applicable	Potentially serious limitations	• Within-cohort study analysis (same paper) • Comparative costing • Population: People diagnosed with PHPT who underwent	2−1: £637 3-1: £100 3-2: cost saving £537[(c)]	n/a	n/a	No sensitivity analysis conducted.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			parathyroidectomy • Comparators: 1. No intraoperative PTH assay 2. Rapid intraoperative PTH assay 3. Delayed intraoperative PTH assay Follow-up: 1 month				

Abbreviations: PTH: parathyroid hormone.
(a) Italian resource use (2000-2015) and unit costs (assumed 2015) data may not reflect current NHS context. QALYs not used as outcome measure.
(b) Analysis is based on a retrospective cohort study. Within-study analysis and so does not reflect full body of evidence. No exploration of uncertainty.
(c) 2015 Euros converted to 2015 UK pounds[354]

1.5.4 Unit costs of pre-operative imaging

Table 17: UK costs of non-invasive imaging techniques

Type of imaging	Description	Cost
Ultrasound	Ultrasound Scan with duration of less than 20 minutes, without Contrast	£52
Sestamibi	Nuclear Medicine Parathyroid scan	£189
SPECT	Single Photon Emission Computed Tomography with Computed Tomography (SPECT-CT) of One Area, 19 years and over	£270
SPECT/CT	Single Photon Emission Computed Tomography with Computed Tomography (SPECT-CT) of One Area, 19 years and over	£284
CT	Computerised Tomography Scan of One Area, without Contrast, 19 years and over	£86
	Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over	£98
	Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	£121
MRI	Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over	£162

Source: NHS Reference costs 2016-17[118]

Table 18: UK costs of invasive imaging techniques

Type of imaging	Description	Cost
Parathyroid venous sampling	Selective venous sampling, including scan, day stay and blood sample costs	£1,320

Source: Estimate from one NHS Trust

1.5.5 Health economic analysis for intra-operative imaging

An exploratory analysis was conducted to consider whether the use of a rapid intra-operative parathyroid hormone (IOPTH) test during parathyroidectomy could be justified on an economic basis. This analysis sought to answer two questions:

1. What is the improvement in probability of successful surgery required to make IOPTH testing during a parathyroidectomy cost neutral?
2. What is the improvement in quality of life required following successful surgery to make IOPTH testing during a parathyroidectomy cost effective?

A detailed write up of this analysis is available in appendix I.

The results of the exploratory analysis indicate that including IOPTH testing during parathyroidectomy is highly unlikely to be cost-neutral, as the required improvement in probability of surgical cure attributable to IOPTH testing is too large to be realistic. Results also show that the required improvement in quality of life following successful surgery is higher than can be realistically expected for successful cure of PHPT, therefore IOPTH testing during a parathyroidectomy is highly unlikely to be cost effective.

1.6 Resource impact

The recommendations made in this review are not expected to have a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

1.7.1.1 MIBI+ US pre-operative localisation versus no pre-operative localisation (first operation stratum) (test and treat studies)

There was no difference between MIBI+US pre-operative localisation and no pre-operative localisation for the outcomes normocalcaemia (1 study; n=99; follow up 6 months; Moderate quality); and adverse event of transient recurrent nerve paralysis (1 study; n=99; follow up 6 months; Very Low quality).

No evidence was identified for HRQOL, mortality, success (cure)/ failure, BMD of the distal radius or the lumbar spine; deterioration of renal function, fractures; length of hospital stay; occurrence of kidney stones; reoperation; unnecessary neck exploration.

1.7.1.2 US pre-operative localisation versus no pre-operative localisation (first operation stratum) (test and treat studies)

There was clinically important benefit of US pre-operative localisation for cure (no missed glands and normocalcaemia) (1 study; n=28; follow up 12 months; Very Low quality).

There was no difference between US pre-operative localisation and no pre-operative localisation for length of hospital stay (days) (1 study; n=28; follow up 12 months; Very Low quality).

No evidence was identified for HRQOL, mortality, adverse events, BMD of the distal radius or the lumbar spine; deterioration of renal function, fractures; occurrence of kidney stones; reoperation; unnecessary neck exploration.

1.7.1.3 Diagnostic accuracy of imaging localisation tests in people with first time surgery stratum (diagnostic accuracy studies)

One study showed that ultrasound had a sensitivity of 87% (CI 74% to 95%) and a corresponding specificity of 0% (CI 0% to 84%) (n=49; Very Low quality).

Seven studies showed that MIBI had a sensitivity range of 78-98% and a corresponding specificity range of 0-100% (n=274; Very Low quality).

Three studies showed that MIBI subtraction had a sensitivity range of 88-100% and a corresponding specificity range of 0-100% (n=81; Very Low quality).

Four studies showed that MIBI (SPECT) had a sensitivity range of 61-100% and a corresponding specificity range of 92-100% (n=88; Very Low quality).

One study showed that MIBI (SPECT/CT) had a sensitivity of 89% (CI 65% to 99%) and a corresponding specificity of 60% (CI 15% to 95%) (n=10; Very Low quality).

One study showed that MRI had a sensitivity of 90% (CI 55% to 100%) (n=10; Low quality). Corresponding specificity was not estimable.

One study showed that SPECT +US had a sensitivity of 98% (CI 94% to 100%) and a corresponding specificity of 0% (CI 0% to 52%) (n=127; Very Low quality).

There was no evidence for the sensitivity and specificity of CT scanning in people undergoing first time surgery.

1.7.1.4 Diagnostic accuracy of imaging localisation tests in mixed first and re-operation stratum (diagnostic accuracy studies)

Three studies showed that ultrasound had a sensitivity range of 64-68% and a corresponding specificity range of 33-71% (not estimable in one study) (n=114; Very Low quality).

Three studies showed that MIBI had a sensitivity range of 64-97% and a corresponding specificity range of 57-100% (not estimable in one study (n=104; Very Low quality).

One study showed that MRI had a sensitivity of 50% (CI 7% to 93%) (corresponding specificity non-estimable) (n=4; Very Low quality).

One study showed that CT had a sensitivity of 33% (CI 1% to 91%) (corresponding specificity non-estimable) (n=3; Very Low quality).

There was no evidence for the sensitivity and specificity of MIBI subtraction, MIBI SPECT, MIBI with SPECT/CT for mixed first and re-operation stratum.

1.7.1.5 Diagnostic accuracy of imaging localisation tests in a re-operation stratum (diagnostic accuracy studies)

One study showed that MIBI had 100% (CI 40% to 100%) sensitivity in participants undergoing re-operation. Corresponding specificity was not estimable (n=4; Low quality).

1.7.1.6 Intra-operative localisation tests: IOPTH versus no IOPTH in first operation stratum (test and treat studies)

There was no difference between IOPTH and no intra-operative localisation for normocalcaemia (1 study, n=40; follow up 6 months; Moderate quality) and post-operative complications (1 study, n=40; follow up 6 months; Very Low quality) in patients having first time surgery.

No evidence was identified for HRQOL, mortality, success (cure)/ failure, BMD of the distal radius or the lumbar spine; deterioration of renal function, fractures; length of hospital stay; occurrence of kidney stones; reoperation; unnecessary neck exploration

1.7.1.7 Diagnostic accuracy of intra-operative tests in first operation stratum (diagnostic accuracy studies)

Twenty six studies showed that IOPTH had a pooled sensitivity of 97.1% (CI 95.5% to 98.5%) for >50% drop at ≤ 10 minutes and a corresponding specificity of 86.8% (CI 73.7% to 96.7%) (n=4726; Very Low quality).

Seven studies showed that IOPTH had a sensitivity range of 94%-100% and a corresponding specificity range of 50-100% (not estimable for two studies) for a >50% drop at > 10 minutes (n=762; Very Low quality).

Four studies showed that IOPTH had a sensitivity range of 97%-100% and a corresponding specificity range of 93-100% for >50% drop at 10 minutes, (n=417; Low quality).

Two studies showed that frozen section had a sensitivity range of 94%-100% and a corresponding specificity of 22% (n=108; Moderate quality)

1.7.1.8 Diagnostic accuracy of IOPTH in mixed first and re-operation stratum (diagnostic accuracy studies)

Two studies showed that IOPTH had a sensitivity range of 82%-92% and a corresponding specificity of 0-75% for >50% drop at ≤ 10 minutes (n=172; Very Low quality).

No evidence was available for IOPTH >50% drop at >10 mins and IOPTH >50% drop at 10 minutes, plus 20 minute sample in people without a drop at 10 minutes.

1.7.1.9 Diagnostic accuracy of IOPTH in re-operation stratum (diagnostic accuracy studies)

One study showed that IOPTH had a sensitivity of 100% (29% to 100%) for >50% drop at ≤ 10 minutes. Corresponding specificity not estimable (n=3; Very Low quality).

No evidence was available for IOPTH >50% drop at >10 mins and IOPTH >50% drop at 10 minutes, plus 20 minute sample in people without a drop at 10 minutes.

1.7.2 Health economic evidence statements

- One cost-comparison analysis found non-invasive preoperative imaging using SPECT/CT to result in an overall saving of £91 when compared to using SPECT. This study was assessed to be partially applicable with potentially serious limitations.
- One cost-comparison analysis found both rapid intraoperative PTH assay to be the most costly option (£637 more per patient than no intraoperative PTH, and £537 more than delayed PTH). This study was assessed to be partially applicable with potentially serious limitations.
- One original exploratory threshold analysis found that for IOPTH testing during parathyroidectomy to be cost neutral, IOPTH testing needs to improve the probability of successful surgery by 11.3%. It also found that for IOPTH testing during parathyroidectomy to be cost effective at the £20,000 threshold, there needs to be a gain of 2.02 QALYs per additional patient cured. This study was assessed to be directly applicable with potentially serious limitations.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The diagnostic measures that matter most

The evidence was divided into two sections, firstly to address the clinical effectiveness of the localisation tests in predicting the location of abnormal tissue and secondly to address the clinical effectiveness of intra-operative tests (intraoperative parathyroid hormone [IOPTH] and intra-operative frozen sections) to predict correct excision of abnormal tissue and therefore termination of surgery. For each section, evidence was sought from both test-and-treat RCTs and diagnostic accuracy studies. Standard diagnostic accuracy methods could not be used due to the fact that each person has more than 1 parathyroid gland and therefore more than 1 possible outcome within the 2x2 table. Therefore, an adjusted 2x2 table method was used to assess the accuracy of the localisation tests; this is described in section 1.4.1.1. The 2x2 table method used to assess the accuracy of the intra-operative tests is also described in section 1.4.1.2.

For the randomised controlled trial (RCT) test-and-treat evidence the committee considered the outcomes of health-related quality of life, mortality and success (cure) / failure of surgery as critical outcomes for decision making. Other important outcomes included adverse events, bone mass density (BMD) of the distal radius or the lumbar spine, deterioration in renal function, fractures (vertebral or long bone), length of hospital stay, occurrence of kidney stones, persistent hypercalcaemia, reoperation and unnecessary neck exploration.

For the localisation tests, the method chosen allows the accuracy of the tests to be determined according to whether the imaging test would have predicted the correct surgical approach in each person (focused surgery or exploratory surgery). By this method, sensitivity

and specificity would not have the same interpretation as in a standard diagnostic review. Sensitivity and specificity could be interpreted as follows:

- Sensitivity = % of people who have a single adenoma, who are correctly picked up by imaging tests (also the % of people who would get correctly applied focused surgery).
- Specificity = % of people who should get exploratory surgery (final diagnosis is >1 adenoma or hyperplasia), that do (imaging shows no adenoma, hyperplasia or double adenoma).

An index test with a low sensitivity may mean that more people end up getting exploratory surgery who could have had focused surgery (if imaging shows more adenomas then there actually are), or it may mean more people having failed surgery (if imaging shows the incorrect location of a single adenoma, although sometimes this may be picked up during the surgical procedure). An index test with a low specificity may mean that more people would fail focused surgery and have persistent primary hyperparathyroidism (as imaging would predict a single adenoma but they actually have >1).

Both the sensitivity and the specificity of the test were considered equally important by the committee. Although a low specificity would result in more failed surgeries and therefore would appear to be the more important measure, around 85% of people with primary hyperparathyroidism only have a single adenoma, therefore the sensitivity of the test was deemed equally important.

The intra-operative tests of IOPTH and intra-operative frozen sections are not used to aid localisation of the affected tissue, but rather are used to determine whether all the affected tissue has been excised and whether surgery can be terminated. Therefore the method of assessing accuracy of these tests is different to the localisation tests (see section 1.4.1.2). By this method, sensitivity and specificity could be interpreted as follows:

- Sensitivity = the ability to identify people who have had all adenomas removed
- Specificity = the ability to identify people who have remaining abnormal tissue

An index test with a low sensitivity may result from a high proportion of people not having a drop in the IOPTH even when all abnormal tissue has been removed and therefore may result in continuing to explore other glands unnecessarily if the decision to terminate surgery is based on the IOPTH alone. An index test with a low specificity may result from a high proportion of people having a drop in the IOPTH even though there is still abnormal tissue remaining, and therefore if the decision to terminate surgery is based on the IOPTH alone, the surgery would be terminated and the person would remain hypercalcaemic and require further surgery.

1.8.1.2 The quality of the evidence

Clinical evidence for the effectiveness of pre-operative sestamibi+US was available from one test-and-treat RCT, however evidence was only available for two outcomes: normocalcaemia and adverse events. Evidence was of moderate and very low quality for these outcomes, respectively. The outcome of normocalcaemia is synonymous with the critical protocol outcome of cure. No evidence was available for the other protocol outcomes, including the critical outcomes of HRQOL and mortality. Clinical evidence for the effectiveness of pre-operative US (ultrasound) was also available from 1 test-and-treat RCT. Again, evidence was only available for 2 outcomes: cure and length of hospital stay. For both outcomes, evidence was very low quality due to risk of bias and imprecision. No evidence was available for the other protocol outcomes, including the critical outcomes of health-related quality of life (HRQOL) and mortality. The committee noted that the Kairaluoma study was published in 1994 and therefore the US equipment and techniques may have developed and changed since that study was conducted. Test-and-treat studies were not available for all the other pre-operative tests listed in the protocol.

The majority of the evidence for the diagnostic accuracy of the different pre-operative imaging tests was of low or very low quality, making the accuracy of the tests less clear. The measure of specificity was particularly imprecise due to the low numbers of people in the studies with a final outcome of multigland disease. Therefore, the committee focused largely on the sensitivity of the tests which they considered to be representative of what is seen in the whole population. The committee also made recommendations based on current clinical practice and their expert opinion. For first-time surgery, no evidence was available for the following tests: computerised tomography (CT), four-dimensional computed tomography (4DCT), methylene blue or magnetic resonance imaging (MRI).

Clinical evidence for the effectiveness of IOPTH was available from 1 test-and-treat RCT, however evidence was only available for 2 outcomes: normocalcaemia and post-operative complications. Evidence was of Moderate quality. The outcome of normocalcaemia is synonymous with the critical protocol outcome of cure. No evidence was available for the other protocol outcomes, including the critical outcomes of HRQOL and mortality.

The majority of the evidence for the diagnostic accuracy of intra-operative tests was of low or very low quality, with the exception of the evidence for intra-operative frozen sections which was Moderate quality.

1.8.1.3 Benefits and harms

Evidence from the test-and-treat RCTs suggested a clinical benefit of using pre-operative US on the outcome of cure (no missed glands and normocalcaemia) There was no clinical difference in the length of hospital stay with the use of pre-operative US, however the committee noted the long length of hospital stay in both the intervention and control groups which is not representative of durations that would be seen today. There was no clinical difference in outcomes following pre-operative localisation with sestamibi+US. However, the committee noted the high success rate (people achieving normocalcaemia) in the control group. In this study, the control group received a bilateral operation with visualisation of all glands. This is reflective of the high success rate of 4-gland exploration seen in practice. There was no clinical difference in the adverse events between groups and the committee noted that the adverse event of transient recurrent nerve paralysis reported in the study was a very rare event. No clinical evidence was identified for all the other protocol outcomes, including the critical outcomes of HRQOL and mortality. Additionally, no evidence was identified for the other pre-operative localisation tests listed in the protocol, therefore the committee was not able to make a comparison of the different tests from RCT evidence. The committee used evidence of the accuracy of the tests alongside the RCT evidence when discussing the recommendations. All evidence from test-and-treat studies was in people undergoing first-time surgery.

When assessing the accuracy of the tests for correctly identifying all abnormal tissue, the committee was interested in both the sensitivity and specificity of the test as detailed above. However, the measure of specificity was extremely variable between studies and often imprecise. This may reflect the fact that the proportion of people with a final outcome of multigland disease is lower and small numbers contributed to the calculation of specificity. The committee took this into account when discussing the evidence. All pre-operative imaging tests showed a reasonably high sensitivity for first-time surgery. No evidence was available for the following tests for first-time surgery: CT, 4DCT, methylene blue or MRI. Evidence in people undergoing re-operation was limited, with only a small subgroup from one study available for the re-operation alone stratum, and evidence only for the sestamibi test.

Evidence from the test-and-treat RCTs suggested no clinical difference in outcomes with the use of IOPTH. Again, the committee noted the high success rate (people achieving normocalcaemia) in the control group. This is reflective of the high success rate of 4-gland exploration seen in practice. In this study, the control group received a bilateral operation with visualisation of all glands. Perhaps a more useful comparison would have been for the

control group to have surgery terminated on the basis of the pre-operative imaging, without IOPTH or visualisation of all glands. There was no clinical difference in the post-operative complications between groups. No clinical evidence was identified for all the other protocol outcomes, including the critical outcomes of HRQOL and mortality.

Evidence from accuracy studies showed a very high sensitivity of IOPTH and a moderately high specificity, for use in first-time operations. The majority of the evidence was for an IOPTH criteria of a drop of 50% or more from baseline at ≤10 minutes post-excision. However, longer timepoints of up to 20 minutes showed a similar sensitivity, although specificity may be decreased. Four studies assessed the drop at 10 minutes, but for people without a drop at 10 minutes they also looked at the delayed response at 20 minutes. This criteria again gave a similar sensitivity and a higher specificity. Evidence in people undergoing re-operation was limited, with only a small subgroup from one study available for the re-operation alone stratum. This showed a sensitivity of 100%, but specificity was not estimable.

The committee discussed that the purpose of preoperative imaging is to help guide the surgical approach, and not to decide whether to proceed with surgery. There was limited evidence on preoperative imaging so the committee also used their clinical knowledge and experience to make the recommendations.

The committee discussed whether pre-operative imaging was necessary in all people – for example, in people who prefer to have 4-gland exploration or if a decision has already been made to perform 4-gland exploration. Expert opinion was that 4-gland exploration can be marginally more effective than focused surgery. In addition, current techniques of 4-gland exploration only involve a very small incision and slightly longer operation time (around 15 minutes longer), and do not differ greatly from focused surgery. The committee discussed that pre-operative imaging is engrained in current practice. In addition, there are some people (for example people with a concurrent nodular goitre) in whom, without pre-operative localisation, surgery would be difficult and the abnormal parathyroid tissue may not be found. It may also be beneficial in people who have had previous neck surgery. In addition, localisation can often give the surgeon more confidence, as it is reassuring for a surgeon to have some indication of where the disease is likely to be. This is especially true for surgeons in non-specialist centres who may perform less than 10 parathyroid surgeries per year. Pre-operative imaging can marginally decrease an operation time. It can also be reassuring for the patient to have some information about the location of their adenoma prior to their surgery.

The committee discussed that current practice for first-time parathyroid surgery is usually ultrasound and sestamibi, with concordance being necessary to proceed to focused surgery. However, some surgeons are happy to proceed to focused surgery on the basis of a single localisation test; either US or sestamibi alone. The advantage of US is that it does not involve any exposure to radiation, and if performed correctly, it can provide very good results. However the committee considered that US is very operator dependent and ideally should be performed by a head and neck radiologist. They therefore allowed for sestamibi to be used where the expertise is not available to perform ultrasound.

The committee agreed that, in first-time surgery, first pre-operative imaging (usually US) should be performed followed by a second imaging modality, if it will further inform surgery, depending on the feasibility and availability of the imaging technique. The committee noted that most centres use sestamibi however some centres do use 4DCT. The committee from their experience felt that the performance and radiation dose exposure for 4DCT and sestamibi were similar. The committee discussed the value of 4DCT but due to lack of evidence did not make a specific recommendation for this technique. However they highlighted that both of the above radiation modalities should not be used together. The committee was of the view that various imaging techniques such as conventional 2D/3DCT were also used but the imaging quality was not as good as 4DCT. The committee noted that

the advantage of dual scanning is that US and sestamibi/4DCT provide different types of information. US gives anatomical information about the presence of the adenoma, the absence of other adenomas and details of any other thyroid abnormalities. The committee noted that ultrasound is very dependent on the skill of the person performing the test and it was important that the person performing the ultrasound knows where to look for the abnormal glands. Hence in clinical practice, some endocrine surgeons perform their own ultrasound prior to parathyroid surgery for this reason. It was also discussed that although ultrasound is good for identifying glands in the neck, it cannot identify if the diseased glands are located either deep in the neck or in the chest. Sestamibi/4DCT gives functional information about dominant hyper-functioning regions in the neck. They also noted that sestamibi/4DCT has the ability to show ectopic adenomas in the neck. There is evidence that sestamibi has a high sensitivity for localisation of a single adenoma. The advantages of sestamibi scans/4DCT are their ability to evaluate for diseased glands outside of the neck at the same time. Hence when there is a fifth parathyroid gland in an ectopic position; functional imaging will pick it up but not anatomical imaging.

The committee agreed that although dual-scanning using two different imaging modalities has the advantage of providing both anatomical and functional information, a second imaging modality (usually a sestamibi scan) following a first imaging modality (usually a US) should be performed only if further information on surgical approach is required. The committee noted that the thyroid is particularly sensitive to radiation and unnecessary exposure should be avoided. Hence the committee agreed that if both first and second modality scans are performed, concordance from dual-scanning was the desired outcome.

If the first imaging modality is negative then there is no requirement to scan with a second imaging test, and proceeding straight to 4-gland exploration will avoid any unnecessary radiation for the person. The committee agreed that in a situation of positive first imaging modality but negative second modality scan, a third scan would unlikely add anything and the preferred approach would be to proceed to 4-gland exploration.

The committee agreed that in situations where dual-scanning fails to identify an adenoma or are discordant, further imaging should not be offered as it will not add useful information and will expose the person to unnecessary radiation. The committee agreed that when first imaging and second imaging modality scans are discordant, 4-gland exploration should be considered as the specific anatomical location of the adenoma cannot be assured.

The committee discussed that in current practice IOPTH is used in difficult cases and is not used routinely. They felt that people having 4-gland exploration would gain more from IOPTH as 4-gland exploration would have more complicated cases where the adenoma was not localised and went on to have 4-gland exploration. The committee from their knowledge and experience stated that there was a marginal benefit (0.9%-1.4%) with the use of IOPTH but debated if this was significant. They also noted that this marginal benefit could be partially attributed to surgical expertise. The committee considered that there was not sufficient evidence to recommend IOPTH for first-time surgery.

The committee discussed from their experience that the use of CT in first-time surgery may be as high as 15%. The committee noted that not all hospitals performing parathyroid surgery will have nuclear medicine facilities and in these cases, CT is an option. However, the committee stressed that there is no need to perform both sestamibi and CT, as this would expose the person to further unnecessary radiation.

The committee also discussed that focused surgery may include unilateral surgery, visualising both glands on the side indicated from imaging studies. Persistent primary hyperparathyroidism resulting after a unilateral surgery would be dealt with differently to persistent primary hyperparathyroidism resulting from an unsuccessful 4-gland exploration. Someone with persistent primary hyperparathyroidism following a unilateral surgery would likely have a re-operation without further pre-operative imaging, with visualisation of the glands on the contralateral side to the previous surgery. Someone with persistent primary

hyperparathyroidism following a 4-gland exploration would require further pre-operative imaging prior to re-operation.

The committee discussed that pre-operative localisation strategies for re-surgery should only be determined following an MDT review of the previous imaging and operative findings at a specialist centre. The committee noted that re-imaging should be performed in the centre where re-surgery will be conducted so as to avoid duplication of imaging, reducing radiation exposure and resource use.

The committee considered that people who have had any prior surgery in the neck, for example thyroid surgery, would need more imaging than someone with no history of previous surgery in the neck.

The committee from their experience felt that parathyroid venous sampling should not be used in first-time surgery, but may have a place in re-operative surgery. Venous sampling is an invasive technique involving insertion of a catheter in the femoral vein and selective catheterisation and sampling of PTH in multiple neck and mediastinal veins. With parathyroid venous sampling it is not technically feasible to precisely locate the adenoma, only to lateralise or regionalise the suspected area. As there was no evidence, the committee did not make any specific recommendations for venous sampling.

The committee was concerned that some people were not receiving surgery on the basis of having non-localised disease. It was discussed that some surgeons may be reluctant to take on non-localised disease and it is often reassuring for a surgeon to have some indication of where the disease is likely to be. However, the committee agreed that non-localisation was not a reason not to operate and that people with non-localised disease should receive 4-gland exploratory surgery.

1.8.2 Cost effectiveness and resource use

For pre-operative imaging, the economic evidence review identified one study comparing costs of parathyroid surgery following localisation using single-photon emission computed tomography (SPECT) to that of surgery following localisation using SPECT/CT. This included costs of equipment, diagnostic tests, surgical team, hospitalisation and post-operative care. Intraoperative assays were used to determine the end of the operation in both cases. The study concluded that SPECT/CT provided better focus for surgery and thus a shorter required surgical time, resulting in an overall cost saving of £91 compared to SPECT. This study was assessed as partially applicable with potentially serious limitations. The committee noted that the study was conducted in Italy, and hence resource use and unit cost data may not be reflective of current NHS context. Given the small sample size in this study (55), the committee considered that the results of this study were uncertain.

Unit costs for pre-operative imaging were presented to the committee for consideration. Ultrasound scan was the imaging modality with the lowest cost (£52) while parathyroid venous sampling incurred the highest cost (£1,320). The committee noted that the low cost of the ultrasound is part of the reason – along with consideration for exposure to radiation – that it is generally the first form of imaging they recommended. It was also noted that this initial imaging may help avoid a more costly imaging modality – such as sestamibi scan – where it is not necessary.

The cost-effectiveness of preoperative localisation is contingent on the outcome of surgery – that is, whether a patient is cured. This is also partially dependent on whether intra-operative imaging is undertaken. As such, the committee was unable to assess the cost-effectiveness of preoperative localisation as an independent intervention.

The committee noted that in current practice, patients who have been assessed to be eligible for surgery will undergo pre-operative localisation imaging regardless of whether they eventually receive focused surgery or 4-gland exploration. That is, preoperative imaging is

generally used to inform surgical approach, and not only for localising an adenoma after surgery has been recommended. Consequently, the recommendation of using ultrasound as first-line imaging is in line with current practice, and hence is not expected to have a significant impact on healthcare resource use.

For intra-operative imaging, the economic evidence review identified one study comparing the overall costs of parathyroid surgery using an IOPTH assay to the costs of parathyroid surgery that does not use an IOPTH assay. The IOPTH arm was further divided into delayed and rapid testing. Patients in this study have previously undergone preoperative localisation using sestamibi, ultrasonography, or both. The study included costs relating to the assays, the operating room, as well as costs of reoperation for surgical failures. The study found that surgery using rapid IOPTH was the most expensive at £1,218, followed by surgery using delayed IOPTH at £681. Surgery without IOPTH was the least expensive option at £581. This study was assessed as partially applicable with potentially serious limitations. The committee noted that the study was conducted in Italy; hence resource use and unit cost data may not be reflective of current NHS context, but overall considered that these results were as they expected.

The costs of IOPTH are not listed in the NHS Reference costs, and were estimated by the committee. A standard laboratory-based intraoperative PTH test does not require additional equipment. However, due to the long turnaround time – minimum 30 minutes – and the impracticality of having to wait for the result before the surgery can end, this form of testing is rarely used in real-time current clinical practice. An alternative intraoperative test is the rapid IOPTH, which has a much shorter turnaround time of around 7 minutes. However, this requires expensive machinery, and the committee noted that use of IOPTH is not part of current practice, and most hospitals do not have the necessary equipment to carry it out. From committee estimates, the upfront investment for an analyser machine will cost around £15,000, and each test requires the use of a reagent pack which may cost between £270 and £400.

Given the high cost of IOPTH testing, along with the fact this intervention is not currently used as part of standard practice for parathyroidectomies, the committee identified this area as high priority for original economic analysis. An exploratory threshold analysis was conducted to assess: what improvement in cure rate is required to make testing with IOPTH cost-neutral, and what improvement in quality of life is required to make testing with IOPTH cost-effective.

The results of this analysis showed that, in the base case, the probability of surgical success needed to be improved by 11.3% in order for IOPTH testing to be cost-neutral. Given that the probability of successful surgery without IOPTH tests was reported in the BAETS report to be around 95%, an improvement of this magnitude would not be possible. The results also showed that, in the base case, an additional 2.02 QALYs for each additional person cured is required for IOPTH testing to be considered cost-effective at the £20,000 threshold. As such an improvement is not possible, this result indicates that IOPTH testing is highly unlikely to be cost effective.

A number of scenarios with different assumptions for cost and effectiveness were considered as part of sensitivity analysis. This analysis showed that even with the lowest costs assumed for the IOPTH test and highest costs assumed for a failed operation – that is, highest potential savings from improving probability of surgical success – the probability of surgical success needs to be improved by 5.2% for IOPTH testing to be cost-neutral. While this is lower than the 11.3% required in the base case, it remains outside the possible range of improvement.

Additionally, under the scenario with the most ‘favourable’ conditions for cost effectiveness – lowest costs for IOPTH test, highest costs for a failed operation, and maximum improvement in probability of successful surgery as calculated using the 95% confidence intervals reported in BAETS – there needs to be an improvement of at least 0.23 QALYs per additional person

cured by the end of the first year for IOPTH testing to be considered cost-effective at the £30,000 threshold. The committee was of the consensus that this improvement is still higher than is generally achievable through curing PHPT.

Given that results of the analysis show that IOPTH testing is highly unlikely to be either cost neutral or cost effective, the committee was of the consensus that this intervention should not be recommended in first-time parathyroid surgery. The committee noted that the current reported probability of success in first-time parathyroid surgery is already very high, and given that there is a lack of clinical evidence to show inclusion of the test necessarily leads to an improvement in surgical outcomes, IOPTH testing should not be recommended as part of standard practice.

It was noted that there a several limitations to the BAETS dataset. For example, the data included in the audit is self-reported by surgeons and it is possible outcomes reported may be biased. It is also unclear whether any improvement in the probability of surgical success can be completely attributed to the use of IOPTH testing, as outcomes are not controlled for other factors such as type of surgery or skill level of the surgeon. In reviewing the clinical evidence, only one test-and-treat study was identified to be relevant for this question. This study suggested that the use of IOPTH testing resulted in no clinical difference in surgical outcomes. However, committee consensus was that this study was not representative of the population in question due to methodological quality and small sample size. The committee acknowledged that there remains a level of uncertainty around the results of this analysis, and recommendations were made having taken these into consideration.

1.8.3 Other factors the committee took into account

The committee was aware of the data from the Fifth National audit report by The British Association of Endocrine & Thyroid Surgeons [86]

The audit reported the test rate for the following localisation techniques for first time surgery: nuclear medicine 92.7% (92.2–93.2%), ultrasound 82.8% (82.0–83.5%); CT/MRI 15.3% (14.6–16.0%); venous sampling 2.6% (2.3–3.0%); PET 2.0% (1.8–2.3%); gamma probe 0.4% (0.3–0.6%); methylene blue 14.1% (13.5–14.8%).

In 48% of cases undergoing CT/MRI, the US and sestamibi were negative or discordant. In 36% of cases, however, both US and sestamibi were positive, which raised the question as to the added utility of the cross-sectional imaging. The report suggested that incorporation of CT as part of the nuclear medicine scan (SPECT) could explain some of this effect. In almost all cases undergoing PET scan, ultrasound, sestamibi and CT/MRI were also performed. In 67% of cases undergoing PET scan, the associated sestamibi scan was positive. Use of intra-operative localisation techniques, such as the gamma probe or methylene blue, remained uncommon.

There was a reduction in the proportion of primary hyperparathyroidism cases having surgery without any pre-operative localisation, however there seemed to be an increase in the number of imaging studies undertaken per patient. The report suggested that the main reason to undertake additional imaging was to facilitate a focused approach, so it was interesting to reflect that the rate of focused surgery was almost identical (at around 50%) across the groups having 1, 2, 3 or 4+ modalities of imaging.

The audit reported that for the commonest combination of imaging (sestamibi + US) about 42% of cases had either one or both scans negative, and went on to open/non-focused surgery (presumably bilateral neck exploration); around a further 15% had both scans positive, but went on to open/non-focused surgery (presumably bilateral neck exploration) and this was attributed to discrepancy in exact location of the abnormality between sestamibi and US, or the detection of multigland disease. The remaining patients had focused surgery, with some patients requiring conversion to a standard approach (presumably due to failure to find an adenoma, other intraoperative difficulties such as bleeding, or the discovery of

multigland disease). As with bilateral neck exploration, a small proportion of focused operations did not result in biochemical cure of hypercalcaemia.

The audit reported that during planned focused surgery, only 23.5% of cases were performed using IOPTH. The audit reported that reasons for this low uptake may include the added expense of this investigation, or the time taken to perform PTH analysis, which may extend the length of surgery and impact upon operating theatre scheduling.

When IOPTH was used, however, the conversion rate to conventional surgery (presumably bilateral neck exploration) was higher: 12.0% versus 6.4%. Following conversion there was a slightly higher rate of presumed multigland disease (2 or more glands excised) in the cases performed using IOPTH, although this was not statistically significant. The success rate of surgery (cure of hypercalcaemia) was also slightly improved by the use of IOPTH. The audit reported that IOPTH was also more commonly used (35%) in re-operative, compared to first-time, primary hyperparathyroidism cases. [86]

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Appendices

Appendix A: Review protocols

Table 19: Review protocol: Localisation techniques

Field	Content
Review question	3.1 What is the clinical and cost effectiveness of using non-invasive imaging techniques (for example parathyroid ultrasound, sestamibi scanning, CT and MRI scanning) prior to surgery? 3.2 What is the clinical and cost effectiveness of using invasive imaging techniques (for example parathyroid venous sampling) prior to surgery? 3.3 What is the clinical and cost effectiveness of using intraoperative parathyroid hormone assays, methylene blue and intra operative frozen sections?
Type of review question	Test and treat Diagnostic accuracy
Objective of the review	Localisation techniques are used to localise the adenoma and guide surgery. The objective of the review is to identify the most effective and cost-effective localisation and intra-operative technique

Eligibility criteria – population	Adults (18 years or over) with confirmed primary hyperparathyroidism caused by single adenoma, 4 gland hyperplasia, double adenoma or ectopic adenoma.
	
	Strata:
	• Previous parathyroidectomy (re-operation). Rationale: scarring and distortion of tissue planes plus the potential for ectopic gland location can lead to a lower success rate of pre-operative imaging
	  ○ 1st operation stratum (including studies with ≤5% of population having re-operation)
	  ○ Re-operation stratum (including studies with ≤5% of population having 1st surgery)
	  ○ Mixed/overall (studies including ≥5% re-operation and unable to report results for each subgroup separately; note: analyse 1st and re-operation separately if results reported separately).
	• Pregnant women
	
	Exclude people:
	• with secondary and tertiary HPT
	• with multiple endocrine neoplasia (MEN)
	• with familial hyperparathyroidism
	• with parathyroid carcinoma
	• people on medications interfering with calcium metabolism (for example, lithium).
	
	Studies including mixed populations of people with primary and secondary or tertiary hyperparathyroidism will be excluded unless subgroups reported separately by type of hyperparathyroidism.
	Studies including people with familial hyperparathyroidism, MEN or parathyroid carcinoma will be included if the total proportion of all of these is ≤5% of the study population.

Index tests	**Localisation techniques:**

	Pre-operative imaging using one of the following and read by a radiologist or surgeon • US imaging using a high frequency probe, 10-15 MHz. • US imaging using a high frequency probe combined with colour Doppler ultrasound • Technetium 99m- Sestamibi scanning (planar) using single isotope dual phase scan (uses a single isotope and early and delayed phase imaging, usually at about 10-30 minutes and at 90-120 minutes) • Technetium 99m- Sestamibi scanning (planar) using dual isotope subtraction scan (uses isotope, 99 Tc sestamibi to image the parathyroids and either 123 Iodine or 99 Tc pertechnatate to image the thyroid, and then one set of images is subtracted from the other - often performed with early and delayed imaging) • Three-dimensional sestamibi scanning (also known as planar+ or SPECT) • SPECT-CT • MRI • 4DCT • CT • Parathyroid venous sampling (also called selective parathyroid venography and venous sampling): an interventional radiology technique • Methylene blue (performed intra-operatively but used to image the parathyroid glands and locate the adenoma in the same respect as other pre-operative imaging techniques). **Intra-operative techniques:** • Intra-op frozen sections • IOPTH monitoring (peripheral venous measurements, with pre-incision, pre-gland ligation, and 5,10, and 20 minutes post-gland ligation measurements) using PTH assay as confirmation of gland resection **Exclude:** Thalium technetium scanning; PET scanning; point shear wave elastography; intra-op gamma probe; radionucleotide probe; 3D sonography; US-guided fine-needle aspiration.
Eligibility criteria –reference (gold) standard	1. A gland can be deemed normal (negative for adenoma) if it has been: a. explored and deemed normal by a surgeon (only possible if 4-gland exploration and not MIP) and the person showed cure/normocalcaemia** after removal of another gland. ***OR*** b. if it is not explored (for example if only focused surgery was performed) but the person showed cure/normocalcaemia** after removal of another gland ***OR*** c. excised and histology shows no pathology or the person is not cured** (note: it would be rare to do biopsy and histology on all glands, and need to prove all other glands except the adenoma are normal). 2. A gland can be deemed abnormal (positive for adenoma) if: a. it has a positive histology ***OR*** b. if the patient shows cure/normocalcaemia after its removal**. **The timepoint at which biological cure (normocalcaemia) should be measured is 6 months – normocalcaemia for up to 6 months proves the person does not have persistent PHPT.
Outcomes and prioritisation	**For test and treat review** • HRQOL (continuous outcome) (critical)

- Mortality (dichotomous outcome) (critical)
- Success (cure) / failure (dichotomous outcome) (critical)
- Adverse events (bleeding (return to theatre), severe hypocalcaemia (define),hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) (dichotomous outcome) (important)
- BMD of the distal radius or the lumbar spine (continuous) (important)
- Deterioration in renal function (dichotomous – study may also report renal replacement) (important)
- Fractures (vertebral or long bone) (dichotomous outcome) (important)
- Length of hospital stay (continuous outcome) (important)
- Occurrence of kidney stones (dichotomous outcome) (important)
- Persistent hypercalcaemia (dichotomous outcome) (important)
- Reoperation (dichotomous outcome) (important)

Unnecessary neck exploration (dichotomous outcome) (important)

For diagnostic accuracy review

Target condition (for localisation studies): correct localisation of adenoma (correctly localises the region/quadrant from which an abnormal gland is removed [rather than just the scan correctly identifies hyperactive tissue anywhere, or correctly lateralises the hyperactive gland]).

Target condition (for intra-operative tests): correct prediction of removal of all abnormal tissue.

Outcomes of interest:

Specificity

Sensitivity

Following 2x2 table method used for localisation studies (for full explanation see the methods chapter)

		By the reference standard there was a single adenoma	
		YES	NO
Index test –		True positive (correct application of focused surgery) - imaging identifies a single adenoma location correctly	False positive (either focused surgery would fail or would convert to exploratory) - Imaging shows a single adenoma but there is actually a double adenoma - Imaging shows a single adenoma but there is actually hyperplasia - single on imaging but nothing found
		False Negative - nothing on imaging so single adenoma missed (do another imaging or exploratory surgery) - Imaging incorrectly identifies the location of a single adenoma (either surgery would fail or would convert to exploratory) - multiple findings on imaging but only a single located	True Negative (correct application of exploratory surgery) - Imaging shows nothing and there are no adenomas found - Imaging correctly identifies hyperplasia - Imaging correctly identifies double adenoma - Imaging shows nothing but there is actually a double - Imaging shows nothing but there is hyperplasia - Imaging shows multiple glands but not all in hyperplasia
	TOTAL	***Number of people with a single adenoma / should have focused***	***Number of people who should have exploratory surgery (either as no adenomas, hyperplasia or double adenomas).***

Using this method:

- Sensitivity = % of people who have a single adenoma, who are correctly picked up by imaging tests (also the % of people who would get correctly applied focused surgery).
- Specificity = % of people who should get exploratory surgery (final diagnosis is >1 adenoma or hyperplasia), that do (imaging shows no adenoma, hyperplasia or double adenoma).

Following 2x2 table method used for intra-operative tests (for full explanation see the methods chapter)

		Reference standard	
		+ve	-ve
Index test	+ve	True positive (>50% fall in PTH and all adenomas removed)	False positive (>50% fall in PTH but not all adenomas removed – person remains hypercalcaemic (up to 6 months) or requires re-op or subsequent glands resected in the same op)
	-ve	False Negative (no fall in PTH but all adenomas removed)	True Negative (no fall in PTH and not all adenomas removed – person remains hypercalcaemic (up to 6 months) or requires re-op or subsequent glands resected in the same op)
	TOTAL	***Reference standard positive***	***Reference standard negative***

In this context:

- Sensitivity = the ability to identify people who have had all adenomas removed
- Specificity = the ability to identify people who have remaining abnormal tissue

For IOPTH, it is possible to calculate the 2x2 table values in different ways for people who had >1 gland removed (i.e. for people with multigland disease). As there will be an IOPTH results after excision of the first gland (if this is negative in people who have remaining abnormal tissue and go on to have further glands excised, then people with MGD will be counted as true negatives) and an IOPTH result after excision of all abnormal glands (if this is positive in people with MGD once all their glands have been removed then people with MGD will be counted as true positives). In some studies, both methods can be calculated as they may report (in people with MGD) a negative IOPTH after excision of their first gland (a true negative due to remaining abnormal tissue), but a positive IOPTH after excision of all the abnormal glands (a true positive if all glands are removed and the person is rendered normocalcaemic). The preferred method for this review is to find the IOPTH accuracy after excision of a single gland or excision of the first gland (in people with MGD). This is because the predominant use of IOPTH is likely to be in focused surgery and the accuracy for predicting whether further abnormal tissue remains. Therefore, if it is possible to calculate both methods from a study, the result after excision of the first gland should be calculated. Sensitivity analysis will be performed if there is heterogeneity (see below).

Eligibility criteria – study design

- RCTs (for test-and-treat)
- Cross-sectional studies / cohort studies / single-gate studies (for diagnostic accuracy)

Other inclusion exclusion criteria

Exclusions:

Non-English language papers

Conference abstracts

Proposed sensitivity / subgroup analysis, or meta-regression

No subgroups to investigate

Sensitivity analyses:

- for localisation tests, sub-selection of people based on the pre-operative imaging may introduce heterogeneity in the results, as it will not be representative of the whole population. Therefore, sensitivity analysis will be performed to stratify results into studies reporting all people (no pre-selection for the study based on imaging), studies only reporting people with a suspected single adenoma from imaging, and studies with negative imaging.
- for IOPTH, perform sensitivity analysis if there is heterogeneity, to only include

	studies which give IOPTH results after excision of the first gland (or in studies where all included participants had single gland disease).
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)	• 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, 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	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 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	For details please see the separate Methods report for this guideline.

studies and exploring (in)consistency	
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 the 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.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 20: 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).[335]

Review question	All questions – health economic evidence
	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). • 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 21: 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

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

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 22: 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

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

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.

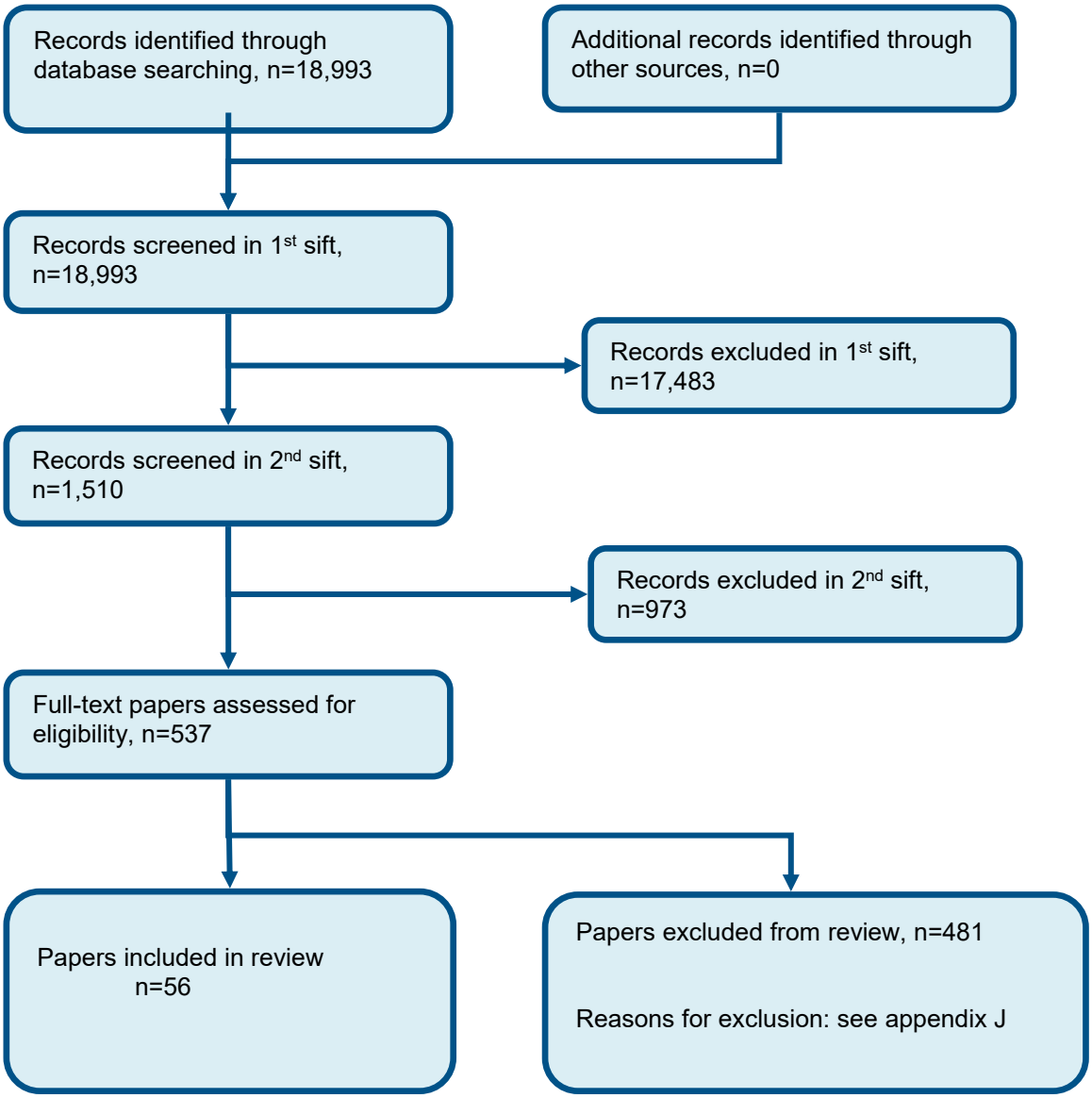
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

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 localisation techniques



Appendix D: Clinical evidence tables

Study	Aarum 2007[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Sweden; Setting: University Hospital
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Verified diagnosis, age ≥50 years, no heredity for hyperparathyroidism or multiple endocrine neoplasia, no concomitant large goitre, no previous thyroid/parathyroid surgery and fitness for day surgery.
Exclusion criteria	Not reported
Recruitment/selection of patients	Recruited from a cohort of patients with an established diagnosis of PHPT referred to our surgical outpatient clinics at Karolinska Hospital and Huddinge University Hospital from October 2000 to March 2004.
Age, gender and ethnicity	Age - Median (range): localisation 64 (46–84); no localisation 62 (50–80). Gender (M:F): localisation 8:41; no localisation 11:39. Ethnicity: not stated
Further population details	n/a
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: preoperative localisation with sestamibi scintigraphy and ultrasonography Treated accordingly (i.e. minimally invasive parathyroidectomy (using an open unilateral approach with a short transverse incision in the middle of the neck under general anaesthesia) was performed in patients in whom both localisation studies were consistent with a single pathological gland, bilateral neck exploration was performed in cases with negative localisation findings, equivocal uptake or positive scintigraphy but negative ultrasonography). Focused surgery performed in 23/50 and bilateral surgery performed in 26/50. All scintigraphic examinations were made according to the double-phase technique using only 99 Tcm-hexakis-2-me- thoxyisobutylisonitrile (99lite®Tcm-MIBI, 99Tcm-sestamibi, Cardio-,DuPont Pharma, Billerica, MA, USA). Three planar and two single photon emission computed tomography (SPECT) images were altogether acquired at 10, 60 and 120 min after IV administration of 500 MBq of the tracer. When

Study	Aarum 2007[1]
	scintigraphy showed an uptake indicating a single pathological gland, the patient was investigated by high resolution ultrasonography of the neck. Indirectness: No indirectness (n=50) Intervention 2: no preoperative localisation All patients underwent conventional bilateral neck exploration with the aim to visualise 4 parathyroid glands and to remove the macroscopically pathological gland(s) Indirectness: No indirectness
Funding	Government (financial support was given by Stockholm County Health Authorities).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Pre-operative localisation with MIBI and US versus no pre-operative localisation Protocol outcome 1: persistent hypercalcaemia - Actual outcome: normocalcaemia at 6months post-operatively; Group 1: 47/49, Group 2: 47/50 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: adverse events - Actual outcome: transient recurrent nerve paralysis; Group 1: 1/49, Group 2: 0/50 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	HRQOL; mortality; success (cure) / failure; BMD of the distal radius or the lumbar spine; deterioration in renal function; fractures (vertebral or long bone); length of hospital stay; occurrence of kidney stones; reoperation; unnecessary neck exploration.

Reference	Agarwal 2012[4]
Study type	Retrospective cohort study
Countries and setting	India; tertiary care referral institute.
Study	Data source: retrieved from a parathyroid disease database

Reference	**Agarwal 2012[4]**				
methodology	Recruitment: data retrieved for patients with sporadic symptomatic PHPT undergoing parathyroidectomy for single parathyroid adenoma (diagnosed based on histology)				
Number of patients	n = 59				
Patient characteristics	Age, mean (range): 36.3 years (range 24-78). Gender (male to female ratio): 18:41 Ethnicity: not reported Inclusion criteria: sporadic symptomatic PHPT undergoing parathyroidectomy for single parathyroid adenoma (diagnosed based on histology). Exclusion criteria: multigland parathyroid disease, parathyroid cancer, renal failure. Details of imaging tests and surgical intervention: people with concordant localisation on ^{99m}Tc-sestamibi and US were offered MIP, the rest were managed with bilateral neck exploration (36 underwent MIP, 23 underwent bilateral). Prior tests: only included people with solitary adenoma (retrospective inclusion from histology) Patient details: n=59 solitary adenoma.				
Index test(s) and reference standard	Index test IOPTH: peripheral blood samples collected pre-operatively, before excision, and 5, 10 and 15 minutes after excision. Serum PTH estimations using an immunoradiometric assay iPTH kit (DSL Inc, Webster, TX, USA). IOPTH results not available to the surgeon intra-operatively so were not used for decision making. Positive = >50% drop in the PTH levels at 10 minutes post-excision compared to the pre-excision value Reference standard Normal serum calcium levels and histology (serum calcium measured at 1 and 3 weeks and then every 3 months).				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	Notes: IOPTH results not available to the surgeon at the time for decision making.
	Index test +	55	0	55	
	Index test −	3	1	4	

Reference	Agarwal 2012[4]				
	Total	58	1	59	
Statistical measures	Index text: IOPTH Sensitivity: 94.8% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none (subselection of people with single gland disease is not a limitation for IOPTH as the index test)				

Reference	Agha 2007[7]
Study type	Retrospective study
Countries and setting	Germany, University Hospital
Study methodology	Data source: not reported Recruitment: patients with PHPT treated in the department between January 2003 and July 2005
Number of patients	n = 58
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: patients with PHPT (PTH>65 ng/l) and increased calcium (>2.6 mmol/l) Exclusion criteria: secondary and tertiary HPT Details of imaging tests and surgical intervention: operative technique based on video-assisted minimal-invasive open approach (MIVAP; n=19) with a 1.5cm incision in the line of Kocher's operation. If per-operative localisation successful, this side opened first. Pre-operative work-up included US and scintigraphy. MRI performed if US and scintigraphy unable to localised pathological tissue. Minimally invasive surgery planned if two out of three methods showed matching results. If lack of corresponding results or inconclusive scintigraphy (n=15), or previous surgery (n=10), or concomitant enlarged goiter (n=14), an open cervical approach was chosen (in which case parathyroid glands explored independent of IOPTH).

<table>
<tr><td>Reference</td><td colspan="5">Agha 2007[7]</td></tr>
<tr><td></td><td colspan="5">Prior tests: no preselection based on prior imaging

Patient details:
n=51 solitary; n=7 multiple
n=10 previous surgery (but parathyroidectomy not specified). Analyse in 1st surgery group.</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
IOPTH: performed with a sandwich assay containing two antibodies (Roche). Measured at the start of anaesthesia (before skin incision) and 10 and 15 minutes after excision.

Positive = >50% drop in the PTH levels at 10 minutes and >60% drop at 15 minutes post-excision compared to the baseline (start of anaesthesia (before skin incision)).

Reference standard
Histology (immediate frozen section by an experienced pathologist) and all patients showed normal serum calcium at follow-up (serum calcium measured at 2 and 6 weeks and 3 and 6 months).</td></tr>
<tr><td>2×2 table</td><td>IOPTH</td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Notes: includes results after continuing to explore and IOPTH after removal of a second site (7 after removal of second site but all eventually had >50% drop and cure). Unable to calculate for >50% drop at 10 minutes for these 7 people.

Study IOPTH criteria also included a >60% drop at 15 minutes, however, no one had a negative IOPTH, so can deduce that that all had the >50% drop at 10 minutes.</td></tr>
<tr><td></td><td>Index test +</td><td>58</td><td>0</td><td>0</td></tr>
<tr><td></td><td>Index test −</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td></td><td>Total</td><td>58</td><td>0</td><td>58</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: IOPTH
Sensitivity: 100%
Specificity: -</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded.
Indirectness: none</td></tr>
</table>

Reference	**Barczynski 2007[34]**
Study type	Prospective cohort
Countries and setting	Poland, Department of Endocrine Surgery, University College of Medicine
Study methodology	Data source: prospective recruitment of patients with PHPT referred for first-time surgery Recruitment: Consecutive patients meeting the inclusion criteria between January 2000 and June 2006
Number of patients	n = 177 (only group 2 (n=115) had IOPTH – results presented here for group 2 only)
Patient characteristics	Age, mean (SD): 57·1 (12·2) years Gender (male to female ratio): 18:97 Ethnicity: not reported Inclusion criteria: biochemically documented pHPT (biochemical evaluation included increased serum calcium >2.6mmol/L and plasma iPTH level >65ng/L) and referred for first-time surgery, at least one localisation study suggesting single parathyroid adenoma, no previous neck surgery and absence of nodular goitre requiring one-step thyroid surgery. Exclusion criteria: a familial history of pHPT (MEN1, MEN2, hereditary pHPT), negative localization studies, suspicion of multiglandular disease, extracervical ectopy, or parathyroid cancer, concomitant nodular goitre, pregnancy or lactation, age below 18 years, high-risk patients with ASA 4 grade (American Society of Anaesthesiology), emergency surgery for hypercalcaemic crisis, and inability to comply with the scheduled follow-up. Details of imaging tests and surgical intervention: MIBI subtraction scintigraphy or high resolution Doppler US performed, at least one of these suggesting single parathyroid adenoma. Underwent MIP (either video-assisted (MIVAP n=64) or open (OMIP n=51)) with IOPTH. Patients with a thyroid gland volume of ≤25 ml assessed by preoperative US, and parathyroid adenoma <30 mm in diameter were qualified for MIVAP; all other patients underwent OMIP. The parathyroid adenoma was located, dissected, removed through a small skin incision and sent for frozen-section examination. The remaining ipsilateral parathyroid gland was electively not exposed but instead, IOPTH was used. Prior tests: suggested single adenoma by at least one imaging (MIBI or US). Patient details: N=105 solitary adenoma, n=5 double, n=4 four gland hyperplasia, n=1 uncured (ectopic later found). All first time surgery
Index test(s)	Index test (IOPTH. Also MIBI and US, but unable to calculate 2x2 table values for protocol method)

Reference	**Barczynski 2007[34]**				
and reference standard	IOPTH: The STAT-IntraOperative-Intact-PTH chemiluminescence immunoassay semiautomated mobile system (Future Diagnostics, Wijchen, the Netherlands) was used within the surgical suite complex for the intraoperative quantitative determination of iPTH levels in EDTA plasma. The following peripheral venous blood samples were analysed: preoperative baseline (before tracheal intubation), pre-excision (after dissection of the adenoma, but before its removal), and 10 min post-excision. Positive = Miami criterion (an iPTH drop of 50% or more from the highest, either preoperative baseline or the pre-excision level at 10 min after gland excision). In patients with an inadequate iPTH decrease at 10 min post-excision, an additional 20 minute estimation made before exploration continued. <u>Reference standard</u> Histology and cure (normal serum calcium values within 6 months of postoperative follow-up). Intraoperative frozen sections were routinely used in both groups to confirm parathyroid tissue origin and to determine the underlying pathology of pHPT (parathyroid adenoma or hyperplasia) according to conventional histopathological criteria.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	Note: method includes taking a 20 minute time point in people with a negative IOPTH at 10 minutes (can also calculate for only 10 minute time point – below) Can calculate both, but this is IOPTH results after excision of the first gland in people with MGD (TNs either went on to have further glands found or were not cured).
	Index test +	105	0	105	
	Index test −	0	10	10	
	Total	105	10	115	
2×2 table	**IOPTH (10 min)**	Reference standard +	Reference standard −	Total	Only including the 10 minute time point result
	Index test +	104	0	104	
	Index test −	1	10	11	
	Total	105	10	115	
Statistical measures	<u>Index text: IOPTH (including 20 minute delayed time point in people without a fall at 10 minutes)</u> Sensitivity: 100% Specificity: 100% <u>Index text: IOPTH (only including 10 minutes)</u> Sensitivity: 99.0% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: none				

Reference	**Barczynski 2007[34]**
	Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).

Reference	**Bobanga 2017[55]**
Study type	Retrospective review
Countries and setting	USA, Surgery department, medical centre.
Study methodology	Data source: prospectively maintained parathyroid database Recruitment: all patients operated on for PHPT by a single surgeon at the centre between May 1994 and February 2016.
Number of patients	n = 127
Patient characteristics	Age, mean (SD): 60 (13) years Gender (male to female ratio): 27:100 Ethnicity: not reported Inclusion criteria: patients operated on for PHPT by a single surgeon; patients with a single focus of abnormal radiotracer accumulation on technetium-99m-sestamibi with SPECT that corresponded to a homogenous, hypoechoic, oval or bean-shaped mass on US exam consistent with an abnormal parathyroid gland. Exclusion criteria: non-concordant pre-operative imaging, no glands seen on pre-operative imaging but adenoma found at exploration; incomplete medical records. Details of imaging tests and surgical intervention: all patients underwent pre-operative imaging with either surgeon-preformed or radiologist-performed neck US and sestamibi with SPECT. Focused surgery performed to explore the site identified on imaging. IOPTH performed in all patients. Prior tests: sub selection of people with concordant imaging SPECT and US predicting a single adenoma. Patient details: n=122 solitary adenoma, n=2 double, n=3 hyperplasia First surgery / re-operation not reported
Index test(s) and reference standard	Index test SPECT + US together (concordant for prediction of a single adenoma)

Reference	**Bobanga 2017[55]**			
	Positive = concordant US and SPECT defined as both studies with radiographic features consistent with a single abnormal parathyroid gland on the same side of the neck and in the same upper or lower location. Reference standard Intraoperative findings. But table 1 states the histopathological findings and text states 'all patients were cured of hyperparathyroidism'.			
2×2 table	**SPECT+US**			All patients had a single adenoma predicted on imaging: Correct localisation of single n=120 (TPs) Incorrect localisation of single n=2 (FNs) Predicted single but final outcome double n=2 (FPs) Predicted single but final outcome hyperplasia n=3 (FPs)
		'True positives' 120	'False positives' 5	
		'False negatives' 2	'True negatives' 0	
	Total	122	5	127
Statistical measures	Index text: SPECT + US 'Sensitivity': 98.4% 'Specificity': 0%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: sub selection of people with concordant imaging SPECT and US predicting a single adenoma			

Reference	**Bonjer 1997[57]**
Study type	Retrospective study
Countries and setting	The Netherlands, University Hospital
Study methodology	Data source: patient records Recruitment: all patients who had operations on the thyroid glands at the University hospital between May 1993 and April 1995.
Number of patients	n = 27 (2/27 had secondary or tertiary HPT, but results reported separately so can exclude from calculations)
Patient characteristics	Age, mean (range): 59 (34-79) years Gender (male to female ratio): 6:21 Ethnicity: not reported

<table>
<tr><td>Reference</td><td colspan="5">Bonjer 1997[57]</td></tr>
<tr><td></td><td colspan="5">Inclusion criteria: hyperparathyroidism confirmed by the findings of raised concentrations of serum parathyroid hormone by a two-site immunoassay; patients with pre-operative sestamibi scans.
Exclusion criteria: patients about to undergo first operation of familial HPT, MEN, and secondary and tertiary HPT.

Details of imaging tests and surgical intervention: patients had MIBI, SPECT and US of the neck and chest. All patients about to undergo their first parathyroidectomy had bilateral exploration (and an attempt made to identify all parathyroid glands). Patients being operated on for persistent or recurrent HPT or patients having local anaesthesia had unilateral exploration.

Prior tests: no preselection based on prior imaging

Patient details:
21 people had primary HPT, 6 people had persistent or recurrent HPT (3 persistent PHPT, 1 recurrent PHPT, and 2 excluded from this analysis due to secondary or tertiary HPT). 16% re-operation, results reported separately for 1st operation (n=21) and re-operation (n=4). n=27 solitary adenoma (n=25 PHPT).</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test (unable to calculate 2x2 table values for US)</u>
<u>MIBI:</u> 99mTc-sestamibi scans done 10, 90 and 150 minutes after 370MBq of 99mTc-sestamibi had been given IV. Anterior and posterior planar images of the neck and chest recorded using a gamma camera with a large field of view and a high resolution parallel-hole collimator.

Positive = not reported

<u>Reference standard</u>
The operative and histopathological findings of those explorations that resulted in normocalcaemia post-operatively (and states in results that all people became normocalcaemic).</td></tr>
<tr><td rowspan="4">2×2 table</td><td>MIBI</td><td></td><td></td><td>Total</td><td rowspan="4">Correct localisation of single n=17 (TPs)
Correct localisation of single in persistent/recurrent PHPT n=4 (TPs)
Incorrect localisation of single n=1 (FNs)
Imaging negative, missed single n=3 (FNs)

Analyse separately for 1st operation (17TPs, 4FNs, n=21) and reoperation (4TPs, n=4).</td></tr>
<tr><td></td><td>‘True positives’
21</td><td>‘False positives’
0</td><td></td></tr>
<tr><td></td><td>‘False negatives’
4</td><td>‘True negatives’
0</td><td></td></tr>
<tr><td>Total</td><td>25</td><td>0</td><td>25</td></tr>
</table>

Reference	Bonjer 1997[57]
Statistical measures	Index text: MIBI 'Sensitivity': 84% 'Specificity': -
Source of funding	Not reported
Limitations	Risk of bias: none Indirectness: none

Reference	Bradley 2016[60]
Study type	Retrospective study
Countries and setting	USA, University Hospital
Study methodology	Data source: not reported Recruitment: meeting criteria between 2007 and 2014
Number of patients	n = 49
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: primary hyperparathyroidism; met consensus criteria for surgical treatment including serum calcium >1mg/dL and elevated PTH levels; studies with 99mTc-sestamibi and US (negative sestamibi scan and a single abnormal gland 0.5cm or greater, suggested on US). Exclusion criteria: Details of imaging tests and surgical intervention: sestamibi and US pre-operatively. IOPTH not used routinely. Forty patients selected for focused neck exploration (involved a unilateral horizontal incision 2-3cm along the anterior border of the sternocleidomastoid). Prior tests: only included people with negative sestamibi scan and US suggesting a single adenoma Patient details:

Reference	**Bradley 2016[60]**				
	First surgery / re-operation not reported				
Index test(s) and reference standard	Index test US: performed 1-2 weeks pre-operatively Positive = not reported Reference standard All 49 people had post-operative normocalcaemia and were considered surgical cures (patients with normalised calcium and final pathology consistent with their operative findings considered surgical cures).				
2×2 table	**US**			Total	All patients had a single adenoma predicted on imaging: Correct localisation of single n=41 (TPs) *(note: in 1 person the localisation was correct but the adenoma wasn't found on the first operation)* Incorrect localisation of single n=6 (FNs) Predicted single but final outcome hyperplasia n=2 (FPs)
		'True positives' 41	'False positives' 2		
		'False negatives' 6	'True negatives' 0		
	Total	47	2	49	
Statistical measures	Index text: 'Sensitivity': 87.2% 'Specificity': 0%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: only included people with negative sestamibi scan and US suggesting a single adenoma				

Reference	**Calo 2013[69]**
Study type	Retrospective study
Countries and setting	Italy, surgical department, university hospital
Study methodology	Data source: not reported Recruitment: undergoing surgery for PHPT in the surgical department between May 2003 and December 2012.
Number of patients	n = 188

<table>
<tr><td>Reference</td><td colspan="5">Calo 2013[69]</td></tr>
<tr><td>Patient characteristics</td><td colspan="5">Age, median (range): 58 (19-85) years

Gender (male to female ratio): 37:202 (total 239 patients including those not undergoing focused)

Ethnicity: not reported

Inclusion criteria: operated on for PHPT in the surgical department; undergoing focused parathyroidectomy; normal renal function.
Exclusion criteria:

Details of imaging tests and surgical intervention: pre-operative tests included MIBI (n=191), US (n=233) and SPECT-CT (n=140). All included patients underwent focused parathyroidectomy. All operations were performed under general anaesthesia with endotracheal intubation and
by the same team of surgeons, who were highly experienced in parathyroid surgery.

Prior tests: only people undergoing focused parathyroidectomy

Patient details:
n=150 solitary, n=35 hyperplasia, n=3 carcinoma (1.6%)
First surgery / re-operation not reported</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
IOPTH: the STAT-Intraoperative-Intact-PTH Chemilluminescence immunoassay semiautomated mobile system (Future Diagnostics, Wijchen, Netherlands) was used within the surgical suite complex for the intraoperative quantitative determination of PTH levels in EDTA plasma.

Positive = Irvin criterion, an intra-operative PTH drop >50% from the highest either pre-incision or pre-excision level after parathyroid excision after 10 minutes (if this didn’t occur within 10 minutes, a PTH drop of >50% from the highest basal value within 20 min after gland excision and/or a residual PTH-20 min level within the reference range)

Reference standard
Post-operative normocalcaemia and PTH, and final histology</td></tr>
<tr><td>2×2 table</td><td>IOPTH
Index test +
Index test −
Total</td><td>Ref standard +
167
6
173</td><td>Ref standard −
1
14
15</td><td>Total
168
20
188</td><td colspan="2">Note: method includes taking a 20 minute time point in people with a negative IOPTH at 10 minutes (can’t calculate for 10 minute time point only)

IOPTH results after excision of the 1st gland only for those who had multiple glands – i.e. for these, was the –ve IOPTH result predictive of either more pathological glands removed, or post-op hypercalcaemia (of</td></tr>
</table>

Reference	**Calo 2013[69]**				
					the people with IOPTH –ve, 10 went on to have more glands removed and 4 remained hypercalcaemic)
Statistical measures	Index text: (including 20 minute delayed timepoint in people without a fall at 10 minutes) Sensitivity: 96.5% Specificity: 93.3%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).				

Reference	**Casas 1994[79]**
Study type	Retrospective study
Countries and setting	Georgia, Department of Surgery, Medical College
Study methodology	Data source: not reported Recruitment: diagnosed with PHPT from January 1989 to September 1992
Number of patients	n = 42 (but only 21 underwent imaging with MIBI and analysed here)
Patient characteristics	Age, mean (range), n=21: 59 (39-87) years Gender (male to female ratio): 5:16 Ethnicity: race (black: white): 9:12 Inclusion criteria: patients diagnostic with PHPT based on intact PTH levels, elevated total and ionised serum calcium levels and accompanying symptoms. Tc-99m-sestamibi group consisted of patients who received pre-operative localisation with Tc-99m-sestamibi and Iodine-123 radionuclide subtraction imaging. Exclusion criteria: Details of imaging tests and surgical intervention: pre-operative localisation with Tc-99m-sestamibi and Iodine-123 radionuclide subtraction imaging. All patients underwent neck exploration in a standardised fashion and attempts made to identify as many

<table>
<tr><td>Reference</td><td colspan="5">Casas 1994[79]</td></tr>
<tr><td></td><td colspan="5">parathyroid glands as could be located with reasonable effort and as surgically indicated.

Prior tests: no preselection based on prior imaging

Patient details:
n=16 solitary, n=1 double, n=4 hyperplasia
First surgery / re-operation not reported</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
MIBI: technetium-99m-sestamibi and Iodine-123 radionuclide subtraction imaging. Oral dose of 14.8MBq of I-123 administered 4 hours before imaging with Tc-99m-sestamibi (IV injection of 148 MBq of Tc-99m-sestamibi and imaging of the neck and upper part of the thorax using a parallel collimator and wide-field of view gamma camera. Subtraction image generated.

Positive = not reported

Reference standard
Histology (biopsies of all glands made) and all 21 patients had normal ionised and total post-operative calcium.</td></tr>
<tr><td>2×2 table</td><td>MIBI (subtraction)</td><td></td><td></td><td>Total</td><td rowspan="4">Correct localisation of single n=14 (TPs)
Predicted multigland but final outcome single n=2 (FNs)
Correct prediction of double n=1 (TNs)
Correct prediction of hyperplasia n=4 (TNs)</td></tr>
<tr><td></td><td>‘True positives’
14</td><td>‘False positives’
0</td><td></td></tr>
<tr><td></td><td>‘False negatives’
2</td><td>‘True negatives’
5</td><td></td></tr>
<tr><td>Total</td><td>16</td><td>5</td><td>21</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: MIBI (subtraction)
‘Sensitivity’: 87.5%
‘Specificity’: 100%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded.
Indirectness: none</td></tr>
</table>

<table>
<tr><td>Reference</td><td>Cayo 2009[85]</td></tr>
<tr><td>Study type</td><td>Prospective</td></tr>
<tr><td>Countries and setting</td><td>USA, Department of Surgery, University Hospital</td></tr>
</table>

Reference	**Cayo 2009[85]**				
Study methodology	Data source: n/a Recruitment: between November 2000 and March 2008, data were prospectively collected on 755 patients with PHPT who underwent parathyroidectomy				
Number of patients	n = 161				
Patient characteristics	Age, mean (range): 58 (18–88 years). Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: patients with PHPT who underwent parathyroidectomy; had multiple gland disease on pathology, had IOPTH Exclusion criteria: not reported Details of imaging tests and surgical intervention: not reported Prior tests: sub selection of those found to have multi gland disease on pathology Patient details: All multigland disease (72 double, 89 hyperplasia) First surgery / re-operation not reported				
Index test(s) and reference standard	Index test IOPTH: PTH samples were collected pre-incision, and then at 5, 10, and 15 min after excision of suspected abnormal parathyroid gland(s). Positive = drop of greater than 50% at 5, 10 or 15 minutes compared to pre-incision Reference standard Clinical cure (normocalcaemic postoperatively and remained so for 6 months). All had pathology as all had multigland disease.				
2×2 table	IOPTH	Reference standard +	Reference standard −	Total	Study states 11 people had TN results (no drop in IOPTH and hypercalcaemic post-operatively), but this included 5 people who had recurrence after 6 months (in other studies, e.g. Chen 2005, this is counted as a cure). Therefore, for this analysis these 5 are counted as FNs (no drop in
	Index test +	146	0	146	
	Index test −	9	6	15	
	Total	155	6	161	

Reference	**Cayo 2009[85]**				
					IOPTH but were normocalcaemic within 6 months).
Statistical measures	Index text: Sensitivity: 94.2% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none				

Reference	**Chen 2005[94]**
Study type	Unclear
Countries and setting	USA, Department of Surgery, Medical School
Study methodology	Data source: not reported Recruitment: consecutive patients with PHPT with positive localisation for a single adenoma and candidates for MIP from January 1990 to June 2004.
Number of patients	n = 345 (only results for group 2 included here, n=188 who had IOPTH)
Patient characteristics	Age, mean (SD), n=188: 60 (3) years Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: PHPT with positive localisation for a single adenoma and candidates for MIP who underwent neck exploration. Exclusion criteria: not reported Details of imaging tests and surgical intervention: minimally invasive parathyroidectomy Prior tests: sub selection of people with positive localisation studies for a single adenoma and candidates for MIP. Patient details:

Reference	**Chen 2005[94]**
	n=170 solitary, n=9 double, n=9 hyperplasia First surgery / re-operation not reported
Index test(s) and reference standard	Index test IOPTH: PTH level drawn from a peripheral vein before operative incision and serves as a baseline. Blood collected in EDTA-containing tubes and loaded on 1 of 2 auto analysers (Elecsys 2010 or the Elecsys 1010 (Roche)). Positive = drop of greater than 50% at 5, 10 or 15 minutes compared to pre-incision Reference standard Surgical cure (calcium less than 10.2mg/dL). No mention of histology in the methods, but in the results it states that people with an initial inadequate drop in IOPTH had subsequent resection of additional 'hyper cellular' parathyroid glands.

2×2 table

	Reference standard +	Reference standard −	Total	
Index test +	170	0	188	Can calculate both, but this is IOPTH results after excision of the first gland in people with MGD (TNs either went on to have further glands found or were not cured).
Index test −	0	18	0	
Total	170	18	188	

Statistical measures	Index text: Sensitivity: 100% Specificity: 100%
Source of funding	NR
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Unclear if histology used as part of reference standard. Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).

Reference	**Chick 2017[96]**
Study type	Retrospective study
Countries and setting	Hong Kong, Department of Surgery, Hospital
Study methodology	Data source: not reported Recruitment: patients who received MIP with selective use of IOPTH for PHPT between March 2006 and June 2015. Historical cohort of patients who received MIP with mandatory IOPTH between March 2002 and February 2006.
Number of	n = 157 (split into 2 groups, group 1 n=100 with optional IOPTH, only 25 had IOPTH and group 2 n=57 with mandatory IOPTH, only 54

Reference	Chick 2017[96]				
patients	had IOPTH. Total having IOPTH n=79 included in this analysis)				
Patient characteristics	Age, mean (SD): selective IOPTH group (n=100) 56.4 (13.9) years, mandatory IOPTH group (n=57) 59.3 (14) years. Gender (male to female ratio): 56:101 (all n=157) Ethnicity: not reported Inclusion criteria: patients with PHPT meeting the inclusion criteria for MIP (at least 1 positive localisation study suggesting a single parathyroid adenoma, and the absence of thyroid nodules or tumours requiring thyroidectomy) Exclusion criteria: presence of a thyroid lesion requiring thyroidectomy, negative localisation, extracervical ectopy, suspicion of multi-gland disease, large sized adenoma, familial history of PHPT (including MEN). Details of imaging tests and surgical intervention: sestamibi and US, other localisation such as CT performed at the discretion of the surgeon. All operations performed under general anaesthesia. MIP was a direct, focused approach using a small cervical incision placed according to the location of the diseased gland from pre-operative US performed by the surgeon. Prior tests: sub selection of people eligible for MIP (at least one localisation study suggesting solitary adenoma) and excluded people with negative imaging or suspicion of multigland disease. For group 2, all people had IOPTH, for group 1 only people with discordant MIBI, US and intraoperative findings received IOPTH). Patient details: First surgery / re-operation not reported				
Index test(s) and reference standard	Index test IOPTH: Immulite 1000 Immunoassay system 2002-2004 (Siemens, Germany), Roche Modular analytics E170 system 2004-2013 (Roche, Switzerland), Roche cobas e411 sytem 2014-2015 (Roche). Blood for PTH assay collected by venepuncture into EDTA tubes from the peripheral vein before skin incision (pre-incision), after dissection of the adenoma but before its removal (pre-excision) and at 10 minutes. Positive = Miami: drop of 50% or more from the highest baseline value (pre-incision or pre-excision) at 10 minutes. If this did not occur then a 20 minute sample taken and a drop of 50% or more at 20 minutes. Reference standard Normocalcaemia at 6 months. No mention of histology in the methods but the results state ‘for the pathology…’				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	Note: method includes taking a 20 minute timepoint in people with a negative IOPTH at 10 minutes (can also
	Index test +	78	0		

Reference	**Chick 2017[96]**				
	Index test −	0	1		calculate for only 10 minute timepoint – below) Group 1: 25TPs, group 2: 53TPs, 1TN IOPTH results after excision of all glands in people with multigland disease
	Total	78	1	79	
2×2 table	**IOPTH (10 mins)**	Reference standard +	Reference standard −	Total	Including 10 minute timepoint only
	Index test +	75	0		
	Index test −	3	1		
	Total	78	1	79	
Statistical measures	Index text: (including 20 minute delayed timepoint in people without a fall at 10 minutes) Sensitivity: 100% Specificity: 100% Index text: (10 minutes only) Sensitivity: 96.2% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).				

Reference	**Garner 1999[153]**
Study type	Unclear
Countries and setting	USA, Department of Surgery, University Medical Centre
Study methodology	Data source: not reported Recruitment: consecutive patients
Number of patients	n = 130
Patient	Age, mean (SD): 56.9 (12.3) years

<table>
<tr><td>Reference characteristics</td><td colspan="5">Garner 1999[153]

Gender (male to female ratio): 29:101

Ethnicity: not reported

Inclusion criteria: not reported
Exclusion criteria: not reported

Details of imaging tests and surgical intervention: not reported

Prior tests: not reported

Patient details:
First surgery / re-operation not reported</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
<u>IOPTH:</u> samples collected from either peripheral or jugular veins or peripheral arteries into EDTA tubes. Plasma samples assayed for PTH by the Nichols Institute Diagnostic QuiCk-IntraOperative Intact PTH Assay, an immunochemiluminometric assay. Pre-incision (after anaesthesia induction), pre-excision (after identification of the gland but before removal) and at 5 and 10 minutes.

Positive = >50% drop at around 10 minutes (although one person had a delayed drop at 24 minutes)

<u>Reference standard</u>
Normal calcium level post-operatively. Pathology not mentioned in the methods but mentions pathological examination in the results.</td></tr>
<tr><td>2×2 table</td><td>IOPTH
Index test +
Index test −
Total</td><td>Reference standard +
122
3
125</td><td>Reference standard −
3
2
5</td><td>Total
126
4
130</td><td colspan="2">Narrative comment ‘of the cases that fell <50% after 10 minutes, one fell after a longer time interval (24 minutes)’ (however, methods don’t state that the 20 minute time point was routinely assessed if there was no drop at 10 minutes, therefore analysed as a FN (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute time point taken).

IOPTH results after excision of all glands in people with multigland disease</td></tr>
</table>

Reference	Garner 1999[153]
Statistical measures	Index text: Sensitivity: 98.4% Specificity: 40%
Source of funding	Not reported
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none

Reference	Hamilton 1988[181]
Study type	Prospective
Countries and setting	USA, University Hospital
Study methodology	Data source: n/a Recruitment: not reported
Number of patients	n = 10
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: positive diagnosis required an elevated serum calcium on at least 2 separate occasions and an elevated C-terminal PTH level measured by radioimmunoassay. Exclusion criteria: malignancy, sarcoidosis, vitamin D intoxication and idiopathic hypocalciuric hypercalcaemia. Details of imaging tests and surgical intervention: MRI. Operative approach consisted of a transverse cervical incision. Systematic exploration performed with careful attention devoted to the region containing the suspected enlarged gland. Prior tests: no preselection based on prior imaging Patient details: All had solitary adenoma

Reference	**Hamilton 1988[181]**				
	No patient had previous exploration of the neck				
Index test(s) and reference standard	Index test MRI: General electric 1.5 tesla superconducting magnet. Spin echo images utilising both short and long repetition times and echo time. Images acquired in the axial plane in all cases. Coronal and sagittal imaging obtained selectively to assist localising. Positive = not reported Reference standard Normal post-op calcium levels confirmed successful resection in all cases and no patient required a secondary operation. All glands biopsied.				
2×2 table	MRI			Total	Correct localisation of single n=9 (TPs) Incorrect localisation of single n=1 (FNs)
		‘True positives’ 9	‘False positives’ 0		
		‘False negatives’ 1	‘True negatives’ 0		
	Total	10	0	10	
Statistical measures	Index text: ‘Sensitivity’: 90% ‘Specificity’ -				
Source of funding	not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none				

Reference	**Hanif 2006[183]**
Study type	Unclear
Countries and setting	Ireland, Department of Surgery, University Hospital
Study methodology	Data source: not reported Recruitment: a cohort undergoing surgery for HPT over a 3 year period.
Number of patients	n = 51
Patient	Age, mean (SD): 63 (14) years

Reference characteristics	Hanif 2006[183]				
	Gender (male to female ratio): 14:37 Ethnicity: not reported Inclusion criteria: patients suitable for minimally invasive radio-guided parathyroidectomy (MIRP) for PHPT; diagnosis of hyperparathyroidism was based on clinical features and confirmed by the findings of high total and/or ionized calcium levels and levels of intact PTH. Exclusion criteria: patients unsuitable for MIRP due to thyroid disease, suspected bilateral multi glandular disease or syndromes causing hyperparathyroidism. Details of imaging tests and surgical intervention: preoperative Tc sestamibi scanning, in the patients with recurrent disease also performed ultrasonography of the neck to support the diagnosis. Each operation was carried out under general anaesthesia using a skin crease transverse cervical incision measuring ≤4 cm (mean, 3.3 – 0.4 cm). A hand-held gamma radiation detecting probe (Navigator RMD Watertown, MA, USA) was used to map the abnormal glands. Prior tests: sub selection of people suitable for MIRP Patient details: 3 re-operation (5.9%) n=46 solitary, n=3 double, n=2 ectopic				
Index test(s) and reference standard	Index test IOPTH: a baseline rapid iPTH level was taken prior to the first incision using a chemiluminescence immunoassay. This measurement detects levels of intact parathyroid hormone in plasma (Future Diagnostics BV, Wijchen, The Netherlands). A venous sample was taken from the antecubital vein using an intravenous 14–16-gauge cannula. This intravenous access was used for rapid iPTH sampling during the procedure. Positive = a post-excision drop in iPTH ≥50% at 5, 10 or 15 minutes relative to the preoperative value Reference standard All the patients that were subsequently followed (with a follow-up range from 3 months to 2 years) were normocalcaemic with normal PTH levels. Histopathology of all glands excised confirmed parathyroid adenomas.				
2×2 table	IOPTH	Reference standard +	Reference standard −	Total	IOPTH results taken after removal of all glands in people with multiple adenomas.
	Index test +	48	0	48	
	Index test −	3	0	3	
	Total	51	0	51	

Reference	**Hanif 2006[183]**
Statistical measures	Index text: Sensitivity: 94.1% Specificity: -
Source of funding	States: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article
Limitations	Risk of bias: none Indirectness: none (sub selection of people for MIRP is not a limitation for IOPTH index test).

Reference	**Harris 2008[186]**
Study type	Prospective
Countries and setting	Canada, Division of Surgery, Health Sciences centre
Study methodology	Data source: n/a Recruitment: all patients referred to the centre for suspected parathyroid adenoma
Number of patients	n = 23
Patient characteristics	Age, median (range): 66 years (26–80) years Gender (male to female ratio): 9:14 Ethnicity: not reported Inclusion criteria: not reported Exclusion criteria: not reported Details of imaging tests and surgical intervention: If SPECT-CT negative then bilateral surgery undertaken with the initial side chosen at random. If SPECT-CT positive, the positive side was explored first. Prior tests: no preselection based on prior imaging Patient details: n=18 solitary, n=2 double, n=3 hyperplasia

<table>
<tr><td>Reference</td><td colspan="5">Harris 2008[186]</td></tr>
<tr><td></td><td colspan="5">First surgery / re-operation not reported</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
SPECT-CT: Patients received 700 MBq of 99m-Tc-sestamibi by intravenous injection. Immediate and 2-hour anterior planar images of the
neck and mediastinum were obtained using a low-energy high resolution (LEHR) large field-of-view gamma camera with a high-resolution parallel hole collimator. SPECT-CT scans spanning from the angle of the mandible to the base of the heart were acquired at 2 hours. Both SPECT and CT images were obtained using the Infinia Hawkeye or the Hawkeye 4 (General Electric Medical Systems). Hybrid SPECT-CT images were obtained in the axial, sagittal, and coronal planes.

Positive = If a parathyroid adenoma was present on the SPECT-CT images, the nuclear medicine physician plotted out its location using 3-dimensional Cartesian X, Y, and Z coordinates.

Reference standard
SPECT-CT prediction of the parathyroid pathology had to be correct, and the surgeon had to find the parathyroid pathology in the exact location predicted by the scan. States ‘after surgery no patient had persistent hypercalcaemia’.</td></tr>
<tr><td>2×2 table</td><td>SPECT-CT</td><td></td><td></td><td>Total</td><td rowspan="4">Correct localisation of single n=16 (TPs)
Incorrect localisation of single n=2 (FNs)
Correct prediction of double n=1 (TNs)
Imaging negative, had double n=1 (TNs)
Predicted single but final outcome hyperplasia n=2 (FPs)
Imaging negative, had hyperplasia n=1 (TNs)</td></tr>
<tr><td></td><td>‘True positives’
16</td><td>‘False positives’
2</td><td></td></tr>
<tr><td></td><td>‘False negatives’
2</td><td>‘True negatives’
3</td><td></td></tr>
<tr><td>Total</td><td>18</td><td>5</td><td>23</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text:
‘Sensitivity’: 88.9%
‘Specificity’: 60.0%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded
Indirectness: none</td></tr>
</table>

<table>
<tr><td>Reference</td><td>Hathaway 2013[189]</td></tr>
<tr><td>Study type</td><td>Prospective study</td></tr>
<tr><td>Countries and setting</td><td>UK, University Hospital (tertiary centre)</td></tr>
</table>

Reference	**Hathaway 2013[189]**				
Study methodology	Data source: n/a Recruitment: patients undergoing parathyroidectomy for single gland disease between January 2004 and March 2011.				
Number of patients	n = 303 (splits into 2 groups subgroups by pre-operative calcium level, but results provided here for both groups together).				
Patient characteristics	Age, median (range): median 64 in both groups, (range 18-89) years. Gender (male to female ratio): 61:242 Ethnicity: not reported Inclusion criteria: patients undergoing parathyroidectomy for single gland disease; had IOPTH Exclusion criteria: parathyroid carcinoma, MEN, missing data, no recorded preoperative or 3 month corrected calcium, no recorded adenoma weight. Details of imaging tests and surgical intervention: pre-operative localisation with MIBI and US. A focused approach was used when either localisation test was positive. A bilateral approach was used when localisation was negative, no tumour was found, or no drop in IOPTH at 10 minutes. Prior tests: sub selection of people with single gland disease, people with more than one gland excised were excluded Patient details: First surgery / re-operation not reported				
Index test(s) and reference standard	Index test IOPTH: samples taken at baseline, pre-excision, and at 5 and 10 minutes using a 2-site chemiluminescent assay (Cambridge Diagnostics Ltd., Ireland). Positive = 50% drop from the highest of either the baseline or pre-excision values (presumably at either 5 or 10 minutes). Reference standard Normocalcaemia at 3 months. No mention of pathology, however only included people who had a single gland removed (therefore normocalcaemia alone can determine whether the gland was responsible or not).				
2×2 table	IOPTH	Reference standard +	Reference standard −	Total	Note: reference standard does not included pathology, but only included people who had a single gland excised so normocalcaemia alone
	Index test +	291	2	293	
	Index test −	9	1	10	

Reference	**Hathaway 2013[189]**				
	Total	300	3	303	as the reference standard is sufficient
Statistical measures	Index text: Sensitivity: 97.0% Specificity: 33.3%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none (sub selection of people with single gland disease is not a limitation for IOPTH index test).				

Reference	**Hindie 1998[197]**
Study type	Prospective study
Countries and setting	France, University Hospital
Study methodology	Data source: n/a Recruitment: consecutive patients referred for surgical management of PHPT.
Number of patients	n = 30
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: referred for first surgery for PHPT; biochemical confirmation of hyperparathyroidism based on accepted diagnostic criteria Exclusion criteria: not reported Details of imaging tests and surgical intervention: standard bilateral neck exploration (except 1 patient had unilateral neck exposure under local anaesthesia. Some normal glands also biopsied. Prior tests: no preselection based on prior imaging

<table>
<tr><td>Reference</td><td colspan="5">Hindie 1998[197]</td></tr>
<tr><td></td><td colspan="5">Patient details:
n=27 solitary (1 ectopic), n=2 double, n=1 three-gland hyperplasia
First surgery reported</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
intravenous injection of 10 MBq 123-iodide and 2-4hr later, 550 MBq 99mTc-sestamibi. Images of both isotopes were acquired simultaneously using two separate energy windows. Results interpreted by the nuclear physician and surgeon before surgery.
Technetium-99m-sestamibi (single tracer, double phase technique): Images of Tc-99m-sestamibi acquired 15 minutes and 120 minutes after tracer injection were visually compared.

Positive = based on visual comparison of the early and late Tc-99m-sestamibi images. A positive double-phase scan for the presence of an enlarged parathyroid was defined as a focal area of increased uptake of 99m-Tc-sestamibi which showed, relative to the surrounding thyroid, either a gradual increase over time or a fixed uptake which persisted on delayed imaging contrary to the uptake in the thyroid tissue which gradually decreases over time.

Index test
Technetium-99m-sestamibi and Iodine-123 (subtraction scanning technique): Images of Tc-99m-sestamibi and I-123 were recorded simultaneously in non-overlapping windows and then subtracted.

Positive = Interpretation of the subtraction scan was based on the early 99m-Tc-sestamibi image, the 123-I image and the computer subtraction image.

Reference standard
None of the patients had persistent or recurrent hypercalcemia after 6-24months of follow-up. Pathology not reported in the methods, but is mentioned in the discussion and also states that some normal glands were biopsied so presume pathology considered in determining final outcome.</td></tr>
<tr><td>2×2 table</td><td>Single tracer</td><td></td><td></td><td>Total</td><td rowspan="4">Correct localisation of single n=21 (TPs)
Predicted double but final outcome single n=1 (FNs)
Imaging negative, had single n=3 (FNs)
Incorrect localisation of single n=2 (FNs)
Correct prediction of double n=2 (TNs)
Predicted single but final outcome hyperplasia n=1 (FPs)</td></tr>
<tr><td></td><td>‘True positives’
21</td><td>‘False positives’
1</td><td></td></tr>
<tr><td></td><td>‘False negatives’
6</td><td>‘True negatives’
2</td><td></td></tr>
<tr><td>Total</td><td>27</td><td>3</td><td>30</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: single tracer
‘Sensitivity’: 77.8%
‘Specificity’: 66.7%</td></tr>
</table>

Reference	**Hindie 1998[197]**				
2×2 table	**Subtraction**			Total	Correct localisation of single n=25 (TPs) Incorrect localisation of single n=1 (FNs) Imaging negative, had single n=1 (FNs) Correct prediction of double n=2 (TNs) Correct prediction of hyperplasia n=1 (TNs)
		'True positives' 25	'False positives' 0		
		'False negatives' 2	'True negatives' 3		
	Total	27	3	30	
Statistical measures	Index text: subtraction 'Sensitivity': 92.6% 'Specificity': 100%				
Source of funding	not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded; unclear if all people had pathology as part of the reference standard. Indirectness: none				

Reference	**Hughes 2011[207]**
Study type	Retrospective study
Countries and setting	USA, University Medical Centre
Study methodology	Data source: single institution database Recruitment: people who underwent parathyroidectomy for PHPT from September 1999 to September 2009.
Number of patients	n = 228 (when include the 'recognised failures' who had an IOPTH drop of <50%). For some of the data in the study, only the n=207 people who had a positive IOPTH were included, but the 2x2 table values calculated here and the PPV given in the study are for total 228.
Patient characteristics	Age, mean, for the n=207 with a positive IOPTH: mean approx. 60 years Gender (male to female ratio), for the n=207 with a positive IOPTH: 39:168 Ethnicity: not reported Inclusion criteria: patients with PHPT found to have multi-gland disease during the course of focused parathyroidectomy. Multi-gland disease defined as a final histologic diagnosis of more than one excised hyper cellular parathyroid gland

<table>
<tr><td>Reference</td><td colspan="5">Hughes 2011[207]</td></tr>
<tr><td></td><td colspan="5">Exclusion criteria: preoperative multiple endocrine neoplasia type 1 (MEN-1) diagnosis, lithium exposure, incomplete IOPTH data, or the presence of recurrent disease. ‘Recognised failures’ who had an IOPTH drop of <50% (part of the exclusion criteria for some analyses in the study, but the 2x2 table values calculated here and the PPV given in the study include these people).

Details of imaging tests and surgical intervention: initially underwent focused parathyroidectomy with IOPTH.

Prior tests: sub selection of people with multigland disease from histology

Patient details:
All multigland disease
Recurrent disease excluded</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
<u>IOPTH:</u> IOPTH data that had been collected from either a cervical or peripheral venous blood draw (sampling site was consistent in individual patients, and the kinetics were determined by comparing the baseline PTH value to the final PTH value). The Immulite Turbo immune chemiluminometric PTH assay (DPC, Los Angeles, CA, USA) was used to determine intact PTH levels.

Positive = ≥50% drop from baseline (the highest of either the pre-incision (after anaesthesia induction) or the pre-excision (just prior to excision) value) at a median of 13 minutes (5-35 minutes). Note: ≥50% drop and into the normal range also reported (not analysed here).

<u>Reference standard</u>
Final histologic diagnosis of more than one excised hyper cellular parathyroid gland. Serum calcium level of ≤10.2 mg/dl more than 21 days postoperatively.</td></tr>
<tr><td>2×2 table</td><td>IOPTH
Index test +
Index test −
Total</td><td>Reference standard +
193
7
200</td><td>Reference standard −
14
14
28</td><td>Total
207
21
228</td><td colspan="2">Note: results are for a >50% decrease (doesn’t matter if falls into the normal range or not).

Results are for IOPTH taken after multiple gland excision</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text:</u>
Sensitivity: 96.5%
Specificity: 50.0%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: none
Indirectness: none</td></tr>
<tr><td>Comments</td><td colspan="5"></td></tr>
</table>

Reference	Hwang 2010[209]
Study type	Prospective study
Countries and setting	USA, Department of Surgery, University Hospital
Study methodology	Data source: n/a Recruitment: consecutive patients undergoing surgery for PHPT at a single institution during a 3 year period from 2006 to 2009.
Number of patients	n = 280 (including both MIBI positive and negative)
Patient characteristics	Age, mean (SD not reported): 57 years Gender (male to female ratio): 76% female Ethnicity: not reported Inclusion criteria: undergoing surgery for PHPT Exclusion criteria: known familial syndrome; prior failed parathyroidectomy; need for concomitant thyroid surgery; lithium or radiation exposure; begun as open procedure due to imaging studies all negative or discordant or indicating multi-gland disease, known mediastinal adenoma or clinical suspicion for carcinoma. Details of imaging tests and surgical intervention: all underwent sestamibi and surgeon-performed US. IOPTH results only used for surgical decision making in the MIBI-negative, US-positive patients due to a higher probability of multigland disease (but results for all patients reported). Patients with any positive localisation study were offered MIP. Prior tests: sub selection of people selected for MIP. Excluded people whose surgery was begun as open procedure due to imaging studies all negative or discordant or indicating multi-gland disease, known mediastinal adenoma or clinical suspicion for carcinoma. Patient details: Prior failed parathyroidectomy excluded
Index test(s) and reference standard	Index test IOPTH: PTH samples drawn from a peripheral venous site pre-operatively, immediately pre-excision and 10 minutes post-excision. Samples analysed using the Elecsys PTH-STAT assay (Roche Diagnostics) in 2006-2007 and the STAT Intra-Operative PTH System (Future Diagnostics) in 2008-2009. Positive = Miami criteria - drop of >50% from highest pre-excision value (pre-operative or immediately pre-excision) at 10 minutes

Reference	**Hwang 2010[209]**				
	Reference standard Eucalcaemia for at least 6 months. Multigland disease confirmed when more than one histologically abnormal gland removed or when they presented with hypercalcaemia within 6 months following removal of a single.				
2×2 table	IOPTH	Reference standard +	Reference standard −	Total	Note: IOPTH results after removal of the first gland (not after removal of multiple glands) – so a TN result is if they went on to have more abnormal glands removed or hypercalcaemia (can calculate both)
	Index test +	247	1	248	
	Index test −	19	13	32	
	Total	266	14	280	
Statistical measures	Index text: Sensitivity: 92.9% Specificity: 92.9%				
Source of funding	Academic (supported by funds from the UCLA Division of General Surgery)				
Limitations	Risk of bias: none Indirectness: none (sub selection of people with at least 1 positive imaging test is not a limitation for IOPTH index test).				

Reference	**Iacobone 2005[210]**
Study type	Prospective study
Countries and setting	Italy, University
Study methodology	Data source: n/a Recruitment: undergoing operation for PHPT between January 2000 and December 2003
Number of patients	n = 102
Patient characteristics	Age, mean (range): 62 (26-81) years Gender (male to female ratio): 19:83 Ethnicity: not reported Inclusion criteria: underwent bilateral neck exploration or targeted parathyroidectomy for PHPT Exclusion criteria: unclearly documented PHPT; incomplete follow-up data; parathyroid carcinoma; previous parathyroid operations; family

<table>
<tr><td>Reference</td><td colspan="5">Iacobone 2005[210]</td></tr>
<tr><td></td><td colspan="5">history of HPT or MEN.

Details of imaging tests and surgical intervention: conventional bilateral neck exploration (n=44) or focused surgery (n=58; either unilateral, video assisted, radio guided, or open minimally invasive approach) according to availability of pre-operative localisation.

Prior tests: no preselection based on prior imaging tests

Patient details:
n=88 solitary, n=2 double, n=12 hyperplasia
Previous parathyroid operation excluded</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
IOPTH: peripheral venous blood samples collected before skin incision and 5 and 10 minutes after excision (additional measurements obtained if 10 minutes sample did not drop by 50%). Two-site immune chemiluminometric assay specific for intact PTH (Immulite Turbo Intact PTH, USA)

Positive = decline of >50% at the last post-excision value from pre-incision.

Frozen section:

Positive = frozen section diagnosis of parathyroid adenoma

Reference standard
IOPTH and frozen section results after excision of first gland and whether it correctly predicted prolonging surgery. Definitive histological diagnosis confirmed by paraffin-embedded sections and if necessary, immune histochemical or special stains were used. States all patients were cured (defined as normalisation of calcium and intact PTH in the early post-operative days and at least 1, 3 and 6 months after operation.</td></tr>
<tr><td>2×2 table</td><td>IOPTH</td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Note: IOPTH and frozen section results after excision of first gland and whether it correctly predicted prolonging surgery</td></tr>
<tr><td></td><td>Index test +</td><td>84</td><td>0</td><td>84</td></tr>
<tr><td></td><td>Index test −</td><td>0</td><td>18</td><td>18</td></tr>
<tr><td></td><td>Total</td><td>84</td><td>18</td><td>102</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: IOPTH
Sensitivity: 100%
Specificity: 100%</td></tr>
<tr><td>2×2 table</td><td>Frozen section</td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td></td></tr>
</table>

Reference	**Iacobone 2005[210]**				
	Index test +	79	14	93	
	Index test −	5	4	9	
	Total	84	18	102	
Statistical measures	Index text: frozen section Sensitivity: 94.0% Specificity: 22.2%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none				

Reference	**Jaskowiak 2002[224]**
Study type	Prospective study
Countries and setting	USA, University teaching hospital.
Study methodology	Data source: n/a Recruitment: consecutive patients undergoing operations for PHPT from December 1, 1999, to November 30, 2000.
Number of patients	n = 57
Patient characteristics	Age, mean (range): 57 (16-81) years Gender (male to female ratio): 14:43 Ethnicity: not reported Inclusion criteria: undergoing operation for PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: bilateral explorations, using a small incision when possible, were performed in first-time operations; most reoperations were unilateral. All operations were performed under general anaesthesia, Preoperative planar dual-phase sestamibi used, and in some cases SPECT.

<table>
<tr><td>Reference</td><td colspan="5">Jaskowiak 2002[224]</td></tr>
<tr><td></td><td colspan="5">Prior tests: no preselection of patients based on prior tests

Patient details:
n=50 solitary (included the one person not cured, presumed to have a single), n=4 double, n=3 multi
6 people with previous operation for HPT (not reported separately) – 12%</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
Technetium Tc 99m sestamibi: dual-phase SPS of the neck and chest with planar images and, in some cases, single-photon emission computed tomography.
Positive = region of uptake on scan.

High resolution real-time ultrasonography: no further details provided
Positive = not reported

IOPTH: Peripheral blood samples were collected via an antecubital intravenous line after the induction of anaesthesia but before the incision (baseline 1); after the incision but before resection of the gland (baseline 2); at excision; and at approximately 5 and 10 minutes after the excision. Additional samples were collected when necessary, particularly when multiple excisions were performed or when qPTH levels did not fall as expected.

Positive = >50% drop from the highest baseline value at 10 minutes (study also reports the following 2 criteria, but >50% drop from highest baseline alone can be calculated from the Nichols criterion: 1. >50% drop from the pre-incision value and return to normal at 10 minutes; 2. Nichols: >50% drop from the HIGHEST baseline value at 10 minutes and an absolute value lower than the lowest baseline level).

Reference standard
Pathology not reported in methods but is mentioned in results and discussion about the histological confirmation of some adenoma (presume histology used to confirm in all patients). Frozen sections of suspected abnormal parathyroid tissue were routinely obtained intraoperatively. 56/57 people were cured (normocalcaemia). The one person not cured was presumed to have a single adenoma.</td></tr>
<tr><td>2×2 table</td><td>MIBI</td><td></td><td></td><td>Total</td><td rowspan="4">Results in study assume that the one person not cured had a single adenoma.

Correctly identified single n=38 (TPs)
Imaging negative, had single n=7 (FNs)
Incorrect localisation of single n=1 (FNs)
Predicted multiple but final outcome single n=4 (FNs)
Predicted single but final outcome double n=2 (FPs)
Predicted single but final outcome hyperplasia n=1 (FPs)</td></tr>
<tr><td></td><td>‘True positives’
38</td><td>‘False positives’
3</td><td></td></tr>
<tr><td></td><td>‘False negatives’
12</td><td>‘True negatives’
4</td><td></td></tr>
<tr><td></td><td>Total</td><td>50</td><td>7</td><td></td></tr>
</table>

Reference	**Jaskowiak 2002[224]**				
					Correctly identifies double adenoma n=1 (TNs) Imaging negative, final outcome double n=1 (TNs) Imaging negative, final outcome hyperplasia n=1 (TNs) Imaging shows multiple glands but not all in hyperplasia n=1 (TNs)
Statistical measures	Index text: MIBI 'Sensitivity': 76.0% 'Specificity': 57.1%				
2×2 table	**US**			Total	Results in study assume that the one person not cured had a single adenoma. Correctly identified single n=32 (TPs) Imaging negative, had single n=13 (FNs) Incorrect localisation of single n=3 (FNs) Predicted multiple but final outcome single n=2 (FNs) Predicted single but final outcome double n=1 (FPs) Predicted single but final outcome hyperplasia n=1 (FPs) Correctly identifies double adenoma n=1 (TNs) Imaging negative, final outcome double n=2 (TNs) Imaging negative, final outcome hyperplasia n=2 (TNs)
		'True positives' 32	'False positives' 2		
		'False negatives' 18	'True negatives' 5		
	Total	50	7		
Statistical measures	Index text: US 'Sensitivity': 64.0% 'Specificity': 71.4%				
2×2 table	**IOPTH (50% drop from highest baseline)**	Reference standard +	Reference standard −	Total	Criterion (Nichols) is for a 50% drop and into the normal range (but results would be the same for only a 50% drop, regardless of whether into the normal range, i.e. all the people with IOPTH -ve are because it didn't drop by at least 50% at 10 minutes). After excision of 1st gland in people with multiple abnormal glands Narrative comment '3FNs had levels of less than 50% of the highest baseline level documented before leaving the operating room at 20 minutes or longer (however, methods don't state that the 20 minute timepoint was routinely assessed if there was no drop at 10 minutes,
	Index test +	45	2		
	Index test −	4	6		
	Total	49	8	57	

Reference	Jaskowiak 2002[224]				
					therefore analysed these 3 as FNs (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute timepoint taken).
Statistical measures	Index text: IOPTH (Nichols) Sensitivity: 91.8% Specificity: 75.0%				
Source of funding	This study was supported in part by the Nathan and Frances Goldblatt Society for Cancer Research, Chicago.				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded; unclear if all people had pathology as part of the reference standard. Indirectness: none				

Study	Kairaluoma 1994[234]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Finland; Setting: University Hospital
Duration of study	Intervention + follow up: at least 1 year
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	No previous surgery
Subgroup analysis within study	n/a
Inclusion criteria	Primary HPT (reports that laboratory investigations were made on entry to the study, but no details of diagnosis criteria reported).
Exclusion criteria	Secondary or tertiary HPT; MEN; prior thyroidectomy for thyroid disease; simultaneous thyroidectomy; previous US localisation; reoperation for HPT; operated on by another surgeon.
Recruitment/selection of patients	All patients with PHPT referred to the clinic for neck exploration. From July 1989 to January 1993.
Age, gender and ethnicity	Age - Mean (SD): group 1: 54 (12) years; group 2: 65 (16) years. Gender (M:F): group 1 5:9; group 2: 4:10. Ethnicity: not reported
Further population details	Proportion of single and multigland disease the same in both groups. Proportion of ectopic disease higher in group 2 (4/14 and 6/14).
Indirectness of population	No indirectness

Study	Kairaluoma 1994[234]
Interventions	(n=14) Intervention 1: results of pre-operative US reported to the surgeon before exploration All patients underwent bilateral exploration performed by the same surgeon. Neck exploration started on the side where US found an enlarged gland. Indirectness: No indirectness (n=14) Intervention 2: exploration without knowledge of pre-operative US localisation results All patients underwent bilateral exploration performed by the same surgeon. Exploration always started on the left hand side. Indirectness: No indirectness
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Pre-operative localisation US versus no pre-operative localisation (not reported to surgeon) Protocol outcome 1: success (cure) - Actual outcome: cure (the failures had missed glands and hypercalcaemia); Group 1: 14/14, Group 2: 12/14 Risk of bias: All domain – Very high, Selection – Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness Protocol outcome 2: length of hospital stay - Actual outcome: length of hospital stay; Group 1: 6.2 (2.2) days, Group 2: 5.8 (2.2) days Risk of bias: All domain – Very high, Selection – Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	HRQOL; mortality; BMD of the distal radius or the lumbar spine; deterioration in renal function; fractures (vertebral or long bone); persistent hypercalcaemia; occurrence of kidney stones; reoperation; adverse events; unnecessary neck exploration.

Reference	Kim 2015[250]
Study type	Retrospective study
Countries and setting	Korea, University Hospital
Study	Data source: database

Reference methodology	**Kim 2015[250]**				
	Recruitment: all patients who underwent parathyroidectomy by a single surgeon for PHPT from 2004 to 2013				
Number of patients	n = 53				
Patient characteristics	Age, mean (SD): 52.8 (15.5) years Gender (male to female ratio): 19:34 Ethnicity: not reported Inclusion criteria: sporadic PHPT Exclusion criteria: familial disease and secondary hyperparathyroidism Details of imaging tests and surgical intervention: preoperative localization was done by both sestamibi scan and ultrasonography. Patients underwent the MIP or the BNE, both using IOPTH. Results of IOPTH only available during surgery if MIBI or US localization studies failed to find the parathyroid adenoma or absence of concordance, otherwise IOPTH results only available post-operatively. Prior tests: no preselection based on prior tests Patient details: First surgery / re-operation not reported				
Index test(s) and reference standard	Index test IOPTH: the baseline of IOPTH level was measured before parathyroid resection and at 5 and 10 minutes after excision. The IOPTH level was determined with an Elecsys 2010 apparatus (Roche Diagnostics Co., Indianapolis, IN, USA). Positive = drop of >50% at 10 minutes Reference standard Normocalcaemia for at least 6 months after operation. Also reports number of single and multiple from pathological examination.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	
	Index test +	51	0	51	
	Index test −	0	2	2	
	Total	51	2	53	

Reference	Kim 2015[250]
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: 100%
Source of funding	Not reported
Limitations	Risk of bias: none Indirectness: none

Reference	Krausz 2006[264]
Study type	Retrospective study
Countries and setting	Israel, Medical Centre
Study methodology	Data source: not reported Recruitment: not reported
Number of patients	n = 36
Patient characteristics	Age, mean (SD): 53 (16) years, (range 18-81 years) Gender (male to female ratio): 11:25 Ethnicity: not reported Inclusion criteria: biochemical evidence of PHPT scheduled for surgery based on National Institutes of Health (NIH) criteria Exclusion criteria: not reported Details of imaging tests and surgical intervention: patients with positive MIBI studies underwent focused exploration at the presumed site of the parathyroid adenoma, as determined by scintigraphy; the abnormal parathyroid gland was excised and sent for frozen section examination. In one of the three centers, an intra-operative PTH assay was used to confirm the completion of surgery, sparing the surgeon and patient the need for a frozen section. Bilateral exploration was pursued only in patients with negative imaging results. Prior tests: no preselection of patients based on prior tests Patient details:

Reference	**Krausz 2006[264]**				
	n=6 re-exploration for persistent HPT (16.7%)				
Index test(s) and reference standard	Index test 99mTc-sestamibi (MIBI): anterior planar images of the neck and chest were acquired for 15 minutes at 10 and 120 minutes after intravenous injection of 555 MBq 99mTc-MIBI using a large field-of-view gamma camera equipped with a parallel-hole collimator. A planar thyroid scan, used for visual subtraction of the early MIBI image, was obtained following injection of 74 MBq 99mTc-pertechnetate in patients showing MIBI uptake in the parathyroid adenoma of intensity similar to that seen in the thyroid gland or in the absence of differential washout on the delayed MIBI scan. Positive = evaluated independently by a team of three nuclear medicine physicians, with differences of opinion solved by consensus. A distinct focus of increased or separate MIBI uptake in the neck or focal uptake in the mediastinum was considered positive for a parathyroid adenoma on scintigraphy. Reference standard Histopathologic confirmation of the surgically removed abnormal parathyroid tissue, with subsequent normalization of serum calcium and PTH levels.				
2×2 table	**MIBI**			Total	Correctly localised single n=33 (TPs) Negative imaging, final outcome single n=1 (FNs) Negative imaging, final outcome hyperplasia n=2 (TNs)
		‘True positives’ 33	‘False positives’ 0		
		‘False negatives’ 1	‘True negatives’ 2		
	Total	34	2	36	
Statistical measures	Index text: MIBI ‘Sensitivity’: 97.1% ‘Specificity’: 100%				
Source of funding	not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	**Kumar 2000[268]**
Study type	Unclear
Countries and setting	UK, Hospital

Reference	**Kumar 2000[268]**
Study methodology	Data source: not reported Recruitment: referred to the unit for surgery for PHPT over a period of 4 years (March 1995 to March 1999)
Number of patients	n = 30
Patient characteristics	Age, median (range): 58 (18-73) years Gender (male to female ratio): 11:19 Ethnicity: not reported Inclusion criteria: referred for surgery for PHPT (referral based on symptomatic hypercalcaemia or asymptomatic patients less than 75 years old, with high serum calcium levels). Exclusion criteria: not reported Details of imaging tests and surgical intervention: pre-operative localisation by sestamibi. Unilateral exploration was adopted as indicated by a positive scan. Prior tests: no preselection based on prior tests Patient details:
Index test(s) and reference standard	Index test 99mTc-sestamibi (MIBI; subtraction): each patient injected with 400MBq of 99mTc-sestamibi intravenously. Planar imaging of the head and neck were acquired with a pin hole collimator attached to the gamma camera. Anterior early images were acquired 10 minutes post-injection and late images acquired 3 hours later. A single view of the mediastinum was obtained to exclude the possibility of ectopic mediastinal adenomas. Immediately after the late image was obtained, the patient was injected with 100MBq of 99mTc-pertechnetate and an additional image acquired 5 minutes later. This allowed the background uptake of sestamibi within the thyroid to be digitally subtracted Positive = findings interpreted by a single radiologist. Reference standard Histology undertaken on all excised glands. States all patients were normocalcaemic after 6 months follow-up.
2×2 table	**MIBI (subtraction)** | | | Total | Correctly localised single n=29 (TPs) Predicted single but final outcome hyperplasia n=1 (FPs)

Reference	**Kumar 2000[268]**				
		'True positives' 29	'False positives' 1		
		'False negatives' 0	'True negatives' 0		
	Total	29	1		
Statistical measures	Index text: MIBI (subtraction) 'Sensitivity': 100% 'Specificity': 0%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	**Lee 2014[276]**
Study type	Retrospective study
Countries and setting	USA, University Medical Centre
Study methodology	Data source: institutional parathyroid surgery database (prospectively maintained surgical endocrinology database that contains data on 1,243 patients who underwent parathyroidectomy from 1998 to 2010). Recruitment: patients diagnosed with sporadic PHPT, underwent MIP from 1998 to 2010 and had a minimum of 6 months follow-up data.
Number of patients	n = 557 (but IOPTH data only used in n=547)
Patient characteristics	Age, mean (SD): operative success (n=538) 60.5 (12.6) years; operative failure (n=19) 64.5 (12.7) years Gender (male to female ratio): 118:439 Ethnicity: not reported Inclusion criteria: diagnosed with sporadic PHPT and undergoing MIP Exclusion criteria: previous parathyroid or thyroid surgery; familial or multiple endocrine neoplasia-related hyperparathyroidism syndrome; secondary or tertiary HPT; initial operation planned bilateral exploration (such as when the disease could not be localised with pre-operative imaging); parathyroid carcinoma; lithium associated hyperparathyroidism.

<table>
<tr><td>Reference</td><td colspan="4">Lee 2014[276]</td></tr>
<tr><td></td><td colspan="4">Details of imaging tests and surgical intervention: initial operation planned MIP according to pre-operative localisation (one or a combination of technetium 99mTc sestamibi imaging, ultrasonography, or four-dimensional computed tomographic scanning).

Prior tests: intended initial operation was a MIP (excluded people when the disease could not be located using pre-operative imaging)

Patient details:
Excluded previous parathyroid or thyroid surgery</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="4">Index test
IOPTH: intact PTH levels from a peripheral blood sample.

Positive = a drop of 50 % or more from the pre-incision value at 10 minutes (also provide data for a 60% and 70% drop)

Reference standard
Eucalcaemia 6 months after parathyroidectomy. MGD was defined as present when more than one abnormal gland (hyperplastic or adenoma on final pathology) was removed at the time of the first operation or when excision of single pathologically abnormal parathyroid gland did not result in operative success.</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td></td><td>Index test +</td><td>513</td><td>8</td><td>521</td></tr>
<tr><td></td><td>Index test −</td><td>15</td><td>11</td><td>26</td></tr>
<tr><td></td><td>Total</td><td>528</td><td>19</td><td>547</td></tr>
<tr><td>Statistical measures</td><td colspan="4">Index text: IOPTH
Sensitivity: 97.2%
Specificity: 57.9%</td></tr>
<tr><td>Source of funding</td><td colspan="4">Supported in part by The MD Anderson Cancer Center Support Grant CA016672.</td></tr>
<tr><td>Limitations</td><td colspan="4">Risk of bias: none
Indirectness: none (sub selection of people for MIP is not a limitation for IOPTH index test).</td></tr>
</table>

<table>
<tr><td>Reference</td><td>Lo 2003[290]</td></tr>
<tr><td>Study type</td><td>Unclear</td></tr>
<tr><td>Countries and setting</td><td>Hong Kong; University Medical Centre</td></tr>
</table>

Reference	**Lo 2003[290]**				
Study methodology	Data source: not reported Recruitment: eligible patients referred to the department from 1999 to 2002				
Number of patients	n = 66				
Patient characteristics	Age, median (range): 55 (30-81) years Gender (male to female ratio): 19:47 Ethnicity: not reported Inclusion criteria: sporadic PHPT (biochemically confirmed) and 1 unequivocally enlarged parathyroid gland on pre-operative imaging (eligible for MIP). Exclusion criteria: negative or multiple localisations on pre-operative imaging; need for concomitant thyroidectomy' presence of nodular goiter; positive history of familial PHPT; history of previous neck surgery. Details of imaging tests and surgical intervention: pre-operative localisation with US and sestamibi. MIP performed under general anaesthesia. Prior tests: only included those suspected of having a single adenoma on imaging and underwent endoscopic assisted surgery. Patient details: All had solitary adenoma History of previous neck surgery excluded				
Index test(s) and reference standard	Index test IOPTH: 2ml aliquot of blood drawn from the peripheral vein after induction. The quick PTH assay was done with a two-site antibody immunochemiluminometric system (Diagnostics Quick-Pak system; Nichals Institute, USA). Positive = drop of >50% from pre-incision value at 10 minutes Reference standard Cured of hypercalcaemia with a medium follow-up of 9 months. Pathology not reported in methods but is mentioned in results that it was used in two patients undergoing bilateral operation. All 66 people had a single adenoma and were cured of hypercalcaemia, (therefore normocalaemia alone can determine whether the gland was responsible or not).				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	Delayed decrease seen in 4 people at 30 minutes (analysed as FNs here as 30 minute
	Index test +	62	0	62	

Reference	**Lo 2003[290]**				
	Index test −	4	0	4	timepoint not included in review protocol).
	Total	66	0	66	
Statistical measures	Index text: IOPTH Sensitivity: 93.9% Specificity: -				
Source of funding	not reported				
Limitations	Risk of bias: none Indirectness: none (sub selection of people suspected to have a single adenoma is not a limitation for IOPTH index test).				

Reference	**Lo 2007[291]**
Study type	Unclear
Countries and setting	Hong Kong; University Medical Centre
Study methodology	Data source: not reported Recruitment: consecutive patients with PHPT planned to have MIP during a 40 month period
Number of patients	n = 100
Patient characteristics	Age, median (range): 55.5 (13-93) years. Note- the inclusion of <18s, but they excluded familial disease Gender (male to female ratio): 30:70 Ethnicity: not reported Inclusion criteria: biochemically confirmed PHPT referred for surgery; unequivocal solitary adenoma by either pre-operative localisation study. Exclusion criteria: recurrent PHPT; familial PHPT or MEN; incomplete localisation study results; MIBI scan negative or showed multiple uptake areas; presence of large palpable nodular goiter; history of previous neck surgery; need for concomitant thyroidectomy or major surgical procedures. Details of imaging tests and surgical intervention: pre-operative localisation with US and sestamibi. MIP performed with a 2 to 2.5cm incision followed by focused exploration with or without the assistance of a videoscope.

Reference	**Lo 2007[291]**				
	Prior tests: only included those suspected of having a single adenoma on imaging and underwent MIP. Patient details: n=98 solitary, n=1 double, n=1 hyperplasia Recurrent PHPT excluded				
Index test(s) and reference standard	Index test: IOPTH: quick PTH assay (no other details provided) Positive = decrease >50% at 10 minutes after excision Reference standard Normocalcaemia during the immediate post-operative period and during a median follow-up of 15 months (range 6-43 months). Final pathology included 98 solitary and 2 multigland disease.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	After excision of first gland only (i.e. in the 2 people with multigland disease, they had a <50% drop after excision of the first gland and went on to have further glands discovered). Delayed decrease seen in 3 people at 30 minutes (analysed as FNs here as 30 minute timepoint not included in review protocol).
	Index test +	93	0	93	
	Index test −	5	2	7	
	Total	98	2	100	
Statistical measures	Index text: Sensitivity: 94.9% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none (sub selection of people suspected to have a single adenoma is not a limitation for IOPTH index test).				

Reference	**Lombardi 2008[292]**
Study type	Retrospective study
Countries and setting	Italy
Study	Data source: medical records

Reference methodology	**Lombardi 2008[292]**				
	Recruitment: eligible patients who were operated on for PHPT between March 2002 and February 2008				
Number of patients	n = 207				
Patient characteristics	Age, mean (SD): 56.9 (14.15) years (range 20-83 years). Gender (male to female ratio): 28:179 Ethnicity: not reported Inclusion criteria: sporadic PHPT who underwent focused parathyroidectomy with IOPTH Exclusion criteria: patients with serum creatinine above the normal range (0.7-1.2 mg/dL) Details of imaging tests and surgical intervention: pre-operative localisation with SPECT and high resolution US. Patients either underwent video-assisted parathyroidectomy or minimally invasive conventional focused approach using central access. Prior tests: selected for focused surgery, suspected single adenoma (by concordant results of US and MIBI) Patient details: N=197 solitary, n=10 double First surgery / re-operation not reported				
Index test(s) and reference standard	Index test IOPTH: blood samples collected peripherally at the ankle at pre-incision, pre-excision (after dissection and just before clamping the suspected affected gland's blood supply) and at 10 and 20 minutes after excision. A point of care chemiluminescence immunoassay system (Stat-Intraoperative-intact PTH, Future Diagnostics, The Netherlands) was used. Positive = Miami criteria: drop ≥50% from the highest basal (pre-incision or pre-excision) at 10 minutes. *Study also includes own criteria, not analysed here as includes a fall into the reference range (negative = <50% drop from the highest baseline (pre-incision or pre-excision) value at 20 minutes and/or a 20 minute value higher than the reference range and/or an increase (>7.5ng/L) from T10 to T20.)* Reference standard Normal post-operative serum calcium. Mentions final histology in the results to confirm single or multiple adenoma.				
2×2 table	**IOPTH (Miami)**	Reference standard +	Reference standard −	Total	

Reference	**Lombardi 2008[292]**				
	Index test +	187	5	192	
	Index test −	10	5	15	
	Total	197	10	207	
Statistical measures	Index text: IOPTH (Miami) Sensitivity: 94.5% Specificity: 50.0%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none (sub selection of people suspected to have a single adenoma is not a limitation for IOPTH index test).				

Study	**Miccoli 2008[313]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: University Hospital
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Unclear method of assessment
Stratum	Overall
Subgroup analysis within study	n/a
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	Undergoing surgery in the department for PHPT between October 2005 and February 2006
Age, gender and ethnicity	Age - Mean (SD): group 1:; group 2:. Gender (M:F): 6:34. Ethnicity: not reported Prior tests: only included patients positive for a single adenoma on pre-operative localisation with US and MIBI
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: parathyroidectomy using the MIVAP technique plus IOPTH (surgical procedure was

Study	Miccoli 2008[313]
	ended when a decrease greater than or equal to 50% of the highest preoperative value was reported) Indirectness: No indirectness (n=20) Intervention 2: parathyroidectomy using the MIVAP technique plus a bilateral endoscopic neck exploration (performed via the same central neck access as the MIVAP, and the surgery ended when all 4 glands visualised and removal of any macroscopically enlarged glands) Indirectness: No indirectness
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IOPTH to determine termination of surgery vs visualising all glands to determine termination of surgery Protocol outcome 1: persistent hypercalcaemia - Actual outcome: normalisation of serum calcium at 6 months; Group 1: 19/20, Group 2: 20/20 Risk of bias: All domain – High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness Protocol outcome 2: adverse events - Actual outcome: post-operative complications (haemorrhage laryngeal nerve palsy, hypocalcaemia); Group 1:0 /20, Group 2: 0/20 Risk of bias: All domain – High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	HRQOL; mortality; success/failure; BMD of the distal radius or the lumbar spine; deterioration in renal function; fractures (vertebral or long bone); occurrence of kidney stones; length of hospital stay; reoperation; unnecessary neck exploration.

Reference	Michel 2013[314]
Study type	Prospective study
Countries and setting	Belgium, referral centre
Study methodology	Data source: n/a Recruitment: consecutive patients with biochemically confirmed PHPT who underwent pre-operative MRI between June 2005 and June 2011.

<table>
<tr><td>Reference</td><td colspan="5">Michel 2013[314]</td></tr>
<tr><td></td><td colspan="5"></td></tr>
<tr><td>Number of patients</td><td colspan="5">n = 58</td></tr>
<tr><td>Patient characteristics</td><td colspan="5">Age, mean (SD): 60 (14) years

Gender (male to female ratio): 17:41

Ethnicity: not reported

Inclusion criteria: biochemically confirmed PHPT who underwent pre-operative MRI
Exclusion criteria: not reported

Details of imaging tests and surgical intervention: all patients had MRI (56 also had sestamibi).

Prior tests: no pre-selection of patients based on prior tests

Patient details:
19 previous neck surgery (but none for previous parathyroidectomy) – analyse in 1st operation</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
<u>IOPTH:</u> no details given in the methods

Positive = drop of >50% and within the normal range at 20 minutes (as all people were IOPTH positive, we can calculate that all fit the review protocol criteria of >50% drop (regardless of whether in the reference range or not).

<u>Reference standard</u>
Eucalcaemia at last follow-up. Histopathological confirmation of abnormal tissue in all patients.</td></tr>
<tr><td>2×2 table</td><td>IOPTH
Index test +
Index test −
Total</td><td>Reference standard +
58
0
58</td><td>Reference standard −
0
0
0</td><td>Total</td><td colspan="2">As all people were IOPTH positive, we can calculate that all fit the review protocol criteria of >50% drop (regardless of whether in the reference range or not).

All at 20 minute time point</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text: IOPTH</u>
Sensitivity: 100%
Specificity: -</td></tr>
<tr><td>Source of</td><td colspan="5">Not reported</td></tr>
</table>

Reference	**Michel 2013[314]**
funding	
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none

Reference	**Miura 2002[317]**
Study type	Retrospective study
Countries and setting	USA; University Hospital
Study methodology	Data source: not reported Recruitment: eligible patients from a series of 242 patients from January 1998 to May 2000 who underwent parathyroidectomy by one surgeon at the department of surgery.
Number of patients	n = 115
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: people with PHPT who had undergone IOPTH; without a family history or multiple endocrine neoplasia; normal renal function Exclusion criteria: not reported Details of imaging tests and surgical intervention: patients having an initial operation underwent bilateral surgery with visualisation of all parathyroid glands. MIBI and US used for pre-operative localisation Prior tests: no preselection based on MIBI and US Patient details: n=88 solitary, n=13 double, n=1 triple, n=12 hyperplasia, n=1 carcinoma (<1%) 9 had prior parathyroidectomy (7.8%)
Index test(s) and reference	Index test IOPTH: two-site immunochemiluminometric method with the Quick-Intraoperative intact PTH assay (Nichols Institute Diagnostics, USA).

Reference	**Miura 2002[317]**
standard	Serum intact PTH values were measured after induction of anaesthesia and again 10 minutes Positive = drop of more than 50% from pre-incision at 10 minutes Reference standard Accuracy for adequate gland excision. States all people had successful operations (defined as cure of hypercalcaemia after operation (mean follow-up 11 months, range 2–28 months)). Abnormal glands confirmed histologically.
2×2 table	IOPTH / Reference standard + / Reference standard − / Total Index test + / 92 / 3 / 95 Index test − / 20 / 0 / 20 Total / 112 / 3 / 115
Statistical measures	Index text: Sensitivity: 82.1% Specificity: 0%
Source of funding	Supported in part by Mt. Zion/Health Systems, Friends of Endocrine Surgery, James Martin Foundation, and Toranomon Hospital, Tokyo, Japan.
Limitations	Risk of bias: none Indirectness: none

Reference	**Morks 2001[321]**
Study type	Retrospective study (come data collected prospectively)
Countries and setting	The Netherlands, non-academic Hospital
Study methodology	Data source: medical records Recruitment: all patients with biochemically proven and surgically treated PHPT treated at the Reinier de Graaf Hospital from August 2002 to December 2007.
Number of patients	n = 65
Patient characteristics	Age, mean (range): 63 (29-84) years Gender (male to female ratio): 15:50

<table>
<tr><td>Reference</td><td colspan="5">Morks 2001[321]</td></tr>
<tr><td></td><td colspan="5">Ethnicity: not reported

Inclusion criteria: biochemically proven PHPT (hypercalcaemia with a concomitant increase or inappropriately high level of serum PTH); IOPTH used for first operation for PHPT
Exclusion criteria: lithium therapy, no iOPTH measurements performed, previously undergone parathyroid gland surgery

Details of imaging tests and surgical intervention: all patients received pre-operative localisation studies consisting of nuclear scintigraphy (99m-Tc-sestamibi scan) and/or ultrasound investigation and/or spiral computed tomography (CT). Conventional neck exploration or MIP performed under general anaesthesia.

Prior tests: no preselection based on prior tests

Patient details:
First time operation for all patients</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
<u>IOPTH:</u> levels were measured before incision after induction of anaesthesia, directly before extirpation of the targeted gland, and 3, 6, 9 and 12 minutes after gland removal. Blood samples taken from peripheral venous catheter. IOPTH assessment was carried out using the Siemens Immulite 2500 analyser. Ethylenediaminetetra-acetic acid (EDTA) plasma was added to beads coated with affinity-purified polyclonal goat anti-bodies directed against PTH 44-84. After washing, affinity-purified polyclonal goat antibodies directed against PTH 1-34 conjugated to a marker enzyme were added and the amount of bound enzyme was measured.

Positive = drop of 50% or more at 12 minutes compared to pre-incision value.

<u>Reference standard</u>
Normocalcaemia for at least 3 months post-operatively. Pathological evaluation done.</td></tr>
<tr><td>2×2 table</td><td colspan="5"><table>
<tr><td>IOPTH</td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Note: includes IOPTH results after excision of the first gland for some people with MGD (e.g. TN could be that IOPTH did not drop and they went on to have further abnormal glands identified or went on to have hypercalcaemia).</td></tr>
<tr><td>Index test +</td><td>55</td><td>1</td><td>56</td></tr>
<tr><td>Index test −</td><td>1</td><td>8</td><td>9</td></tr>
<tr><td>Total</td><td>56</td><td>9</td><td>65</td></tr>
</table></td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text: IOPTH</u>
Sensitivity: 98.2%
Specificity: 88.9%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not reported</td></tr>
</table>

Reference	**Morks 2001[321]**
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none

Reference	**Mozzon 2004[325]**
Study type	Retrospective study
Countries and setting	France, University Surgical Unit
Study methodology	Data source: not reported Recruitment: neck explorations performed for PHPT using intraoperative PTH monitoring from April 2001 to February 2003
Number of patients	n = 268 (but n=263 available for analysis)
Patient characteristics	Age, mean (range): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: undergoing operation for PHPT Exclusion criteria: inadequate data on IOPTH; diagnosis of idiopathic hypercalciuria Details of imaging tests and surgical intervention: unilateral or bilateral neck exploration performed (unilateral performed when there was concordant localization of preoperative imaging, except in cases of goitre, MEN syndrome, and previous neck irradiation. Prior tests: no preselection of patients based on prior tests Patient details: n=7 reoperation (both their first and second case included in the 268) (2.6% - analysed in 1st operation stratum) 4.5% had carcinoma or familial HPT; 3.5% presented with PHPT and chronic renal disease. n=207 unigland disease, n=61 multigland disease
Index test(s) and reference standard	Index test IOPTH: intraoperative PTH levels were measured with a rapid two-site IMCA (Nichols Advantage, Nichols Institute Diagnostics, Saint Clement, CA; normal range in our laboratory, 10–65 pg/mL).

Reference	**Mozzon 2004[325]**				
	Positive = drop >50% from baseline (highest of pre-incision ore pre-excision) at 10 minutes (also reported 5 minute time point, but not extracted as 10 minute timepoint available; also reported 30 minute but not extracted as does not match review protocol). Reference standard Successful parathyroidectomy (normal post-operative serum calcium and phosphorus at follow-up (range 3 days to 22 months)). 'Pathologic diagnosis' reported in methods.				
2×2 table	**IOPTH (10 min)**	Reference standard +	Reference standard −	Total	Note: IOPTH results after excision of all glands in people with multigland disease
	Index test +	242	1	243	
	Index test −	12	8	20	
	Total	254	9	263	
Statistical measures	Index text: IOPTH (10 min) Sensitivity: 95.3% Specificity: 88.9%				
Source of funding	not reported				
Limitations	Risk of bias: none Indirectness: none				

Reference	**Nilsen 2006[343]**
Study type	Prospective study
Countries and setting	Norway, University Hospital
Study methodology	Data source: n/a Recruitment: consecutive patients undergoing surgery for HPT with IOPTH between December 2000 and May 2004.
Number of patients	n = 100
Patient characteristics	Age, mean (range): 55 (22-82) years

Reference	**Nilsen 2006[343]**				
	Gender (male to female ratio): 20:80 Ethnicity: not reported Inclusion criteria: undergoing surgery for PHPT with IOPTH. Diagnosis of PHPT confirmed using serum intact PTH and calcium concentrations pre-operatively. Exclusion criteria: not reported Details of imaging tests and surgical intervention: all patients underwent preoperative tumour localization with a 99m-Tc-sestamibi scintigraphy. With convincing preoperative tumour localization, the surgeon directed the dissection to the anatomical location identified. Prior tests: no preselection of patients based on prior test Patient details: n=93 solitary, n=6 double, n=1 hyperplasia No previous neck explorations				
Index test(s) and reference standard	Index test IOPTH: PTH was measured using an immunochemiluminometric assay (ICMA) from Diagnostic Products Corporation (Immulite turbo intact PTH assay). This assay, like other intact PTH assays, recognizes only intact PTH and very large amino-terminal truncated PTH fragments. All blood samples were obtained from a foot vein in the operating room at the induction of general anaesthesia (baseline) and 5and 10 minutes after excision. Positive = drop of >50% of pre-incision at 5 or 10 minutes Index test MIBI: details not reported Positive = not reported Reference standard Post-operative normocalcaemia (states all patients were normocalcaemic post-operatively). In all patients the excised tissue was sent for pathological analysis.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	IOPTH results after excision of the first gland in people with multigland disease (i.e. TNs include people who went on to have another gland removed).
	Index test +	94	0	94	
	Index test −	0	6	6	
	Total	94	6	100	

Reference	**Nilsen 2006[343]**				
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: 100%				
2×2 table	**MIBI**			Total	Correctly localised single n=88 (TPs) Negative imaging, final outcome single n=5 (FNs) Negative imaging, final outcome double n=1 (TNs) Predicted single but final outcome double n=5 (FPs) Predicted single but final outcome hyperplasia n=1 (FPs)
		‘True positives’ 88	‘False positives’ 6		
		‘False negatives’ 5	‘True negatives’ 1		
	Total	93	7	100	
Statistical measures	Index text: MIBI ‘Sensitivity’: 94.6% ‘Specificity’: 14.3%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	**Nordin 2001[347]**
Study type	Retrospective study
Countries and setting	Australia, Hospital
Study methodology	Data source: records Recruitment: adults who underwent SPECT in the unit for suspected or proven PHPT between 1994 and 1998.
Number of patients	n = 33 (results here for n=32 as 1 person had carcinoma)
Patient characteristics	Age, mean (range): 53 years (29-78 years) Gender (male to female ratio): 19:14 Ethnicity: not reported

<table>
<tr><td>Reference</td><td colspan="5">Nordin 2001[347]</td></tr>
<tr><td></td><td colspan="5">Inclusion criteria: proven PHPT who underwent SPECT
Exclusion criteria: not reported

Details of imaging tests and surgical intervention: not reported

Prior tests: no preselection based on prior tests

Patient details:
n=20 solitary, n=10 hyperplasia, n=2 no pathology detected
“Newly diagnosed PHPT” (no previous surgery)</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
SPECT: IV injection of 99m-Tc-sestamibi (600MBq). Planar images of the neck and thorax acquired at 15 minutes and 2 hours after injection. SPECT of the neck was performed at 30 minutes using an ADAC Vertex with 360° orbit and 64 steps of 5.6°per stop. Planar and SPECT images were interpreted by consensus of 2 experienced physicians.

Positive = adenoma considered present if there was a focal area exhibiting washout delay posterior, lateral or inferior to the thyroid gland.

Reference standard
Surgical and histopathological results. States there were no patients with persistent hypercalcaemia.</td></tr>
<tr><td>2×2 table</td><td>MIBI (SPECT)</td><td></td><td></td><td>Total</td><td rowspan="4">Correctly localised single n=19 (TPs)
Incorrectly localised single n=1 (FNs)
Negative imaging, final outcome hyperplasia n=7 (TNs)
Negative imaging, no pathology found & normocalcaemic n=2 (TNs)
Predicted single but final outcome hyperplasia n=1 (FPs)
Correct prediction of hyperplasia n=2 (TNs)</td></tr>
<tr><td></td><td>‘True positives’
19</td><td>‘False positives’
1</td><td></td></tr>
<tr><td></td><td>‘False negatives’
1</td><td>‘True negatives’
11</td><td></td></tr>
<tr><td>Total</td><td>20</td><td>12</td><td>32</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: MIBI (SPECT)
‘Sensitivity’: 95.0%
‘Specificity’: 91.7%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Author supported by the International Atomic Energy Agency.</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded
Indirectness: none</td></tr>
</table>

Reference	**Orloff 2001[355]**				
Study type	Prospective study				
Countries and setting	USA, Medical Centre				
Study methodology	Data source: n/a Recruitment: consecutive patients undergoing operation for primary HPT				
Number of patients	n = 23				
Patient characteristics	Age, mean range: 33-78 years Gender (male to female ratio): 10:13 Ethnicity: not reported Inclusion criteria: biochemically proven PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: all patients underwent pre-operative sestamibi planar scintigraphy, pre-operative administration of methylene blue and surgical neck exploration. Unilateral or bilateral exploration performed. Prior tests: no preselection based on prior tests Patient details: n=18 solitary, n=2 double, n=3 hyperplasia First surgery / re-operation not reported				
Index test(s) and reference standard	Index test MIBI (planar): Tc-99m-sestamibi scan the day before surgery. Positive = not reported Reference standard Histological confirmation with both frozen section and permanent paraffin-embedded tissue examination. States all patients were cured of hypercalcaemia.				
2×2 table	**MIBI**			Total	Correctly localised single n=17 (TPs)
		‘True positives’	‘False positives’		Negative imaging, final outcome single n=1 (FNs)

Reference	**Orloff 2001[355]**			
		17	1	Negative imaging, final outcome hyperplasia n=1 (TNs) Predicted single but final outcome double n=1 (FPs) Correct prediction of hyperplasia n=1 (TNs) Predicted multiple glands but not all abnormal glands detected n=2 (TNs)
		'False negatives' 1	'True negatives' 4	
	Total	18	5	23
Statistical measures	Index text: 'Sensitivity': 94.4% 'Specificity': 80.0%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	**Ozkul 2015[358]**
Study type	Retrospective study
Countries and setting	Turkey, Training and Research Hospital
Study methodology	Data source: not reported Recruitment: patients who had MIP due to PHPT at the unit between January 2013 and December 2013
Number of patients	n = 11
Patient characteristics	Age, mean (range): 49.23 (27-63) years Gender (male to female ratio): 4:9 Ethnicity: not reported Inclusion criteria: had MIP due to PHPT; biochemically proven PHPT with no previous surgery Exclusion criteria: familial disease; persistent recurrent disease; missing data due to lack of documentation; lacking proper work-up. Details of imaging tests and surgical intervention: imaged by at least 2 modalities, US and 99m-Tc-sestamibi with SPECT. If the imaging was not concordant, MRI, IOPTH or frozen section analysis were requested. All patients underwent MIP under general anaesthesia.

Reference	**Ozkul 2015[358]**				
	Prior tests: all underwent MIP but unclear if only selected people with a particular pre-operative imaging result. Patient details: n=10 solitary, n=1 hyperplasia no previous surgery				
Index test(s) and reference standard	Index test MIBI (SPECT): 99m-Tc-sestamibi with SPECT (no further details reported) Positive = not reported Reference standard Final pathology. 10 people showed normocalcaemia post-operatively, the remaining person had a second operation to confirm final pathology as hyperplasia.				
2×2 table	**MIBI (SPECT)**			Total	Correctly localised single n=10 (TPs) Predicted double, final outcome hyperplasia n=1 (TNs)
		‘True positives’ 10	‘False positives’ 0		
		‘False negatives’ 0	‘True negatives’ 1		
	Total	10	1	11	
Statistical measures	Index text: MIBI (SPECT) ‘Sensitivity’: 100% ‘Specificity’: 100%				
Source of funding	No financial support received				
Limitations	Risk of bias: none Indirectness: none				

Reference	**Patel 1998[365]**
Study type	Prospective study
Countries and setting	USA, academic tertiary care centre
Study methodology	Data source: n/a

Reference	Patel 1998[365]
	Recruitment: consecutive patients undergoing parathyroid exploration for adenoma or hyperplasia between January 1, 1995, and December 31, 1996.
Number of patients	n = 43 (but n=10 with hyperplasia had either secondary or tertiary HPT, so not included in the results below for IOPTH).
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: undergoing parathyroid exploration for adenoma or hyperplasia (diagnosis of hyperparathyroidism was determined biochemically based on serum values of calcium and PTH and urinary calcium levels as well as on clinical symptomatology). Exclusion criteria: not reported Details of imaging tests and surgical intervention: bilateral neck exploration and IOPTH. All patients with primary hyperparathyroidism who were suspected of having a parathyroid adenoma underwent preoperative localization with a technetium-99m sestamibi scan. All patients with suspected parathyroid adenoma underwent a technetium-99m sestamibi–directed unilateral cervical exploration with IOPTH. A contralateral neck exploration and biopsy of at least 1 normal gland was also performed in all patients with adenoma to assess the validity of the IOPTH. Patients with multiple gland hyperplasia underwent standard bilateral cervical explorations with rapid PTH sampling to confirm removal of all hyper functioning parathyroid tissue. Prior tests: no preselection based on prior tests Patient details: n=33 solitary First surgery / re-operation not reported
Index test(s) and reference standard	Index test IOPTH: rapid PTH immunoradiometric assay was developed in the Department of Laboratory Medicine at Geisinger Medical Center through a simple, previously described modification of an intact PTH overnight assay method (Nichols Institute Diagnostics, San Juan Capistrano, Calif). All patients had peripheral venous blood samples obtained at the induction of general anaesthesia and 7 minutes after excision of all suspected hyper functioning parathyroid tissue. Positive = drop of >50% from pre-excision value at 7 minutes Reference standard Post-operative normocalcaemia (minimum 9 month follow-up). Histological confirmation.

Reference	**Patel 1998[365]**			
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total
	Index test +	32	0	
	Index test −	0	1	
	Total	32	1	33
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: 100%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	**Richards 2011[391]**
Study type	Retrospective study
Countries and setting	USA; tertiary referral hospital.
Study methodology	Data source: retrospective review of a prospective database Recruitment: patients who underwent an operation for primary HPT from June 1998 to November 2008 at the Mayo Clinic, Rochester, Minnesota, for people having IOPTH during a primary operation
Number of patients	n = 1882 (results available for n=1750 for IOPTH criteria used)
Patient characteristics	Age, mean (range): 61 (10-97) years (unclear how many <18 years) Gender (male to female ratio): 74.7% women Ethnicity: not reported Inclusion criteria: operation for primary HPT; had IOPTH during primary operation Exclusion criteria: not reported Details of imaging tests and surgical intervention: parathyroid subtraction scintigraphy was performed in 1731 patients (92.0%) and neck ultrasonography was obtained in 581 patients (30.9%). Fourteen patients (0.7%) underwent parathyroidectomy without any imaging.

<table>
<tr><td>Reference</td><td colspan="5">Richards 2011[391]</td></tr>
<tr><td></td><td colspan="5">Patients with imaging results that were highly suspicious for bilateral parathyroid disease underwent bilateral exploration. Those with equivocal imaging results on the contralateral side underwent bilateral exploration when the IOPTH level did not meet curative criteria after a focused exploration. Patients who met the curative criteria after a focused exploration did not undergo bilateral exploration.

Prior tests: no preselection based on prior tests

Patient details:
n=1602 single, n=271 multigland disease
All primary operation
n=28 MEN (1.5%)</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
IOPTH: Blood samples were obtained from the jugular vein, radial artery, or a peripheral vein. The baseline jugular vein samples were obtained either before dissection or after mobilization of the abnormal gland. Peripheral vein samples were obtained pre-incision. Intraoperative PTH levels were measured using a standard immunoradiometric assay with either the Immulite (Diagnostics Product Corporation, Los Angeles, California) or the Roche Cobas e411 (Roche Diagnostics Corporation, Indianapolis, Indiana) analyser.

Positive = ≥50% drop from baseline (either pre-incision or pre-excision) at 10 minutes

Reference standard
Cure (no hypercalcemia at 6 months or longer follow-up confirmed with biochemical results or personal communication of biochemical results via survey or telephone conversation with the patient). Pathology results reported.</td></tr>
<tr><td>2×2 table</td><td>IOPTH</td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Suggests IOPTH results after excision of all glands for people with multigland disease (although if the surgery decided to stop after excision of the first gland, even though the IOPTH result was negative, that result was taken).</td></tr>
<tr><td></td><td>Index test +</td><td>1533</td><td>50</td><td>1583</td></tr>
<tr><td></td><td>Index test −</td><td>62</td><td>105</td><td>167</td></tr>
<tr><td></td><td>Total</td><td>1595</td><td>155</td><td>1750</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: IOPTH
Sensitivity: 96.1%
Specificity: 67.7%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Not reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: none
Indirectness: none</td></tr>
</table>

Reference	**Rossi 2000[397]**
Study type	Unclear
Countries and setting	USA, Medical Centre
Study methodology	Data source: n/a Recruitment: consecutive re-operations for HPT performed by 1 surgeon from February 1999 to February 2000.
Number of patients	n = 11
Patient characteristics	Age, mean (range): 58.3 (35-78 years) Gender (male to female ratio): 5:6 Ethnicity: not reported Inclusion criteria: hypercalcaemia and elevated PTH caused by PHPT; reoperation Exclusion criteria: not reported Details of imaging tests and surgical intervention: pre-operative studies included sestamibi and US in all patients, MRI in 4 patients, CT in 3, parathyroid arteriogram in 1 and selective venous sampling in 1. All patients underwent intraoperative Tc-99m-sestamibi scanning and IOPTH. Prior tests: no preselection based on prior tests Patient details: n=11 All reoperation (but only 8/11 reoperation for PHPT – 73%) – analyse separately for IOPTH (can subgroup for IOPTH as they were all TPs)
Index test(s) and reference standard	Index test IOPTH: intraoperative PTH immunochemiluminescent assay. Plasma from a neck or peripheral vein obtained prior to incision, after the thyroid gland was mobilised, and at 5 and 10 minutes post-excision. Positive = drop of >50% from baseline (unclear if pre-incision or pre-excision) at 5 or 10 minutes. Index test

Reference	**Rossi 2000[397]**				
	MIBI: pre-operatively all patients injected with 15mCi of technetium 99m sestamibi. Early images of the neck and chest were obtained at 3 hours post injection. The distribution of the sestamibi in the early and delayed images were compared. Positive = not reported Index test US: high resolution US Positive = not reported Index test MRI: not reported Index test CT: not reported Reference standard Pathology. States all had low or normal post-operative calcium levels.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	Analyse separately for 1st operation (8TPs, n=8) and reoperation (3TPs, n=3).
	Index test +	11	0	11	
	Index test −	0	0	0	
	Total	11	0	11	
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: -				
2×2 table	**MIBI**			Total	Correctly localised single n=7 (TPs) Negative imaging, final outcome single n=4 (FNs)
		‘True positives’ 7	‘False positives’ 0		
		‘False negatives’ 4	‘True negatives’ 0		
	Total	11	0	11	
Statistical measures	Index text: MIBI ‘Sensitivity’: 63.6% ‘Specificity’: -				
2×2 table	**US**			Total	Correctly localised single n=7 (TPs)

Reference	**Rossi 2000[397]**				
		‘True positives’ 7	‘False positives’ 0		Incorrectly localised single n=2 (FNs) Negative imaging, final outcome single n=2 (FNs)
		‘False negatives’ 4	‘True negatives’ 0		
	Total	11	0	11	
Statistical measures	Index text: US ‘Sensitivity’: 63.6% ‘Specificity’: -				
2×2 table	**MRI**			Total	Correctly localised single n=2 (TPs) Incorrectly localised single n=1 (FNs) Negative imaging, final outcome single n=1 (FNs)
		‘True positives’ 2	‘False positives’ 0		
		‘False negatives’ 2	‘True negatives’ 0		
	Total	4	0	4	
Statistical measures	Index text: MRI ‘Sensitivity’: 50.0% ‘Specificity’: -				
2×2 table	**CT**			Total	Correctly localised single n=1 (TPs) Negative imaging, final outcome single n=2 (FNs)
		‘True positives’ 1	‘False positives’ 0		
		‘False negatives’ 2	‘True negatives’ 0		
	Total	3	0	3	
Statistical measures	Index text: CT ‘Sensitivity’: 33.3% ‘Specificity’: -				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	**Rubello 2006[401]**
Study type	Prospective study
Countries and setting	Italy
Study methodology	Data source: n/a Recruitment: consecutive patients with clinically and biochemically confirmed PHPT were entered in this study between August 2004 and December 2004.
Number of patients	n = 54 (but only n=22 undergone surgery to date, so only 22 included in analysis here).
Patient characteristics	Age, mean (range): 54.8 (46-70) years Gender (male to female ratio): 6:16 Ethnicity: not reported Inclusion criteria: clinically and biochemically confirmed PHPT; eligible for MIRS (evidence at scintigraphy of a solitary adenoma; clear 99mTc-sestamibi uptake in the adenoma measured both at planar and at SPECT imaging) Exclusion criteria: concomitant thyroid nodules; history of familial hyperparathyroidism or multiple endocrine neoplasia; history of neck irradiation; previous thyroid or parathyroid surgery. Details of imaging tests and surgical intervention: all patients underwent the same single-day localisation imaging work-up, consisting of planar 99mTc-pertechnetate/99mTc-sestamibi subtraction scintigraphy as described previously followed by 99mTc-sestamibi SPECT imaging. Ultrasound (US) examination of the neck was also routinely obtained using a high-resolution 10-Mab transducer. Prior tests: only included people with evidence of a solitary adenoma on MIBI Patient details: n=22 solitary adenoma No previous thyroid or parathyroid surgery
Index test(s) and reference standard	Index test IOPTH: intraoperative quick parathyroid hormone (QPTH) assay was routinely measured by immunochemoluminescent assay (Liason, Byk Gulden, Italy). Positive = drop of 50% or more from pre-excision value at 10 minutes.

Reference	**Rubello 2006[401]**				
	Index test MIBI (SPECT): SPECT scintigrams were obtained by a dual-head large-field-of-view (LFOV) gamma camera (e-CAM, Siemens, Hoffman Estates, IL) equipped with parallel-hole, low-energy, high-resolution collimators. Patients were injected with 150 MBq (4 mCi) of 99mTc-Pertechnetate. Twenty minutes later, 400 mg of potassium perchlorate (KClO4) was administered orally to speed the thyroid wash-out of 99mTc-pertechnetate. A 10-min time interval is necessary before KClO4 begins its action on the thyroid. Five minutes later, a 99mTc-pertechnetate thyroid image was acquired. Immediately afterwards, and without moving the patient, 550 MBq (15 mCi) of 99mTc-sestamibi was injected, followed by a flush of saline. After planar imaging SPECT imaging commenced. Positive = not reported Reference standard No persistent PHPT in follow-up (ranging from 6 to 27 months). Definitive histopathology.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	IOPTH results after excision of all glands (as all had solitary adenoma)
	Index test +	22	0	22	
	Index test −	0	0	00	
	Total	22	0	22	
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: -				
2×2 table	**MIBI (SPECT)**			Total	Correctly localised single n=22 (TPs)
		‘True positives’ 22	‘False positives’ 0		
		‘False negatives’ 0	‘True negatives’ 0		
	Total	22	0	22	
Statistical measures	Index text: IOPTH ‘Sensitivity’: 100% ‘Specificity’: -				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: sub selection of people suspected of having solitary adenoma (limitation for imaging but not IOPTH index test)				

Reference	**Saaristo 2002[409]**				
Study type	Prospective study				
Countries and setting	Finland, University Hospital				
Study methodology	Data source: n/a Recruitment: consecutive patients with PHPT on the waiting list for operation				
Number of patients	n = 20				
Patient characteristics	Age, mean (range): 60 (40-77) years Gender (male to female ratio): 3:17 Ethnicity: not reported Inclusion criteria: PHPT (verified by elevated serum ionised calcium and intact PTH concentrations, and low serum phosphatase level). Exclusion criteria: previous neck exploration Details of imaging tests and surgical intervention: pre-operative imaging with sestamibi and intraoperative localisation with a handheld gamma probe. Full collar exploration under general anaesthesia. Attempt made to visualise all 4 parathyroid glands. Prior tests: no preselection based on prior tests Patient details: n=16 solitary, n=4 hyperplasia All first surgery				
Index test(s) and reference standard	Index test MIBI: Tc-99m-sestamibi (740MBq) administered IV. Planar anterior images of the neck and mediastinum obtained using a high resolution parallel hole collimator. Immediate images were obtained 10-15 minutes after injection, and delayed images were taken at 3 hours. Positive = one nuclear medicine physician interpreted all the scans. Reference standard Histological confirmation and states hypercalcaemia normalised in each patient (success of operation assessed by serum ionised calcium 2 months after the operation).				
2×2 table	**MIBI**			Total	Correctly localised single n=13 (TPs)

Reference	**Saaristo 2002[409]**				
		‘True positives’ 13	‘False positives’ 0		Incorrectly localised single n=2 (FNs) Negative imaging, final outcome single n=1 (FNs) Correctly localisation hyperplasia n=4 (TNs)
		‘False negatives’ 3	‘True negatives’ 4		
	Total	16	4	20	
Statistical measures	Index text: MIBI ‘Sensitivity’: 81.3% ‘Specificity’: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	**Sagan 2010[412]**
Study type	Retrospective study
Countries and setting	Poland, Thoracic surgery department, Medical University
Study methodology	Data source: not reported Recruitment: patients who underwent surgery for primary mediastinal parathyroid adenoma with IOPTH at the department from January 1999 to December 2008.
Number of patients	n = 33
Patient characteristics	Age, mean (SD): success at targeted PTx 49.45 (9.4) years; failed at targeted 47.86 (11.24) years Gender (male to female ratio): 20:12 Ethnicity: not reported Inclusion criteria: primary sporadic HPT who underwent surgery for primary mediastinal parathyroid adenoma with IOPTH. Diagnosis of HPT verified by elevated serum calcium and PTH levels. Exclusion criteria: not reported Details of imaging tests and surgical intervention: targeted mediastinal parathyroidectomy through either cervical or thoracic approach

Reference	**Sagan 2010[412]**				
	(site of surgery based on pre-operative imaging). US and sestamibi performed in all patients. Mediastinal work-up performed if cervical imaging negative. If difficulties in locating the adenoma were expected, localisation was aided by handheld gamma probe. Prior tests: no preselection based on prior tests Patient details: n=27 solitary, n=2 double, n=3 hyperplasia All had suspected ectopic adenoma First parathyroid operation				
Index test(s) and reference standard	Index test IOPTH: measured with the Immulite 1000 TURBO intact PTH system (Diagnostic Products, USA) in blood drawn from a peripheral vein. Positive = drop >50% from pre-incision (immediately before surgical incision) at 10 minutes Reference standard Postoperative normalisation of calcium. Pathological examination.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	After excision of first gland in people with multiple glands (can calculate both)
	Index test +	26	0		
	Index test −	0	7		
	Total	26	7		
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none				

Reference	**Sprouse 2001[457]**
Study type	Prospective study
Countries and setting	USA, University Hospital
Study methodology	Data source: n/a

<table>
<tr><td>Reference</td><td colspan="5">Sprouse 2001[457]</td></tr>
<tr><td></td><td colspan="5">Recruitment: all patients presenting with a biochemical diagnosis of PHPT between January 1997 and November 2000</td></tr>
<tr><td>Number of patients</td><td colspan="5">n = 56 (only included people with positive MIBI, this included n=9 who chose a bilateral approach but had pre-operative MIBI anyway).</td></tr>
<tr><td>Patient characteristics</td><td colspan="5">Age, mean (range): in the 47 patients who selected MIP 69.3 (31-89) years

Gender (male to female ratio): in the 47 patients who selected MIP 16:31

Ethnicity: not reported

Inclusion criteria: biochemical diagnosis of PHPT; patients who chose MIP
Exclusion criteria: negative MIBI or suspicion of multigland disease; previous thyroid resection; recurrent or persistent HPT

Details of imaging tests and surgical intervention: included patients who chose to have MIP (n=9 who chose to have a bilateral approach but had pre-operative MIBI data were also included). Patients selecting MIP whose MIBI suggested single gland disease at a specific location underwent a directed exploration after injection of local anaesthetic (at the site indicated by the MIBI)

Prior tests: sub selection of people – excluded people with negative MIBI or suspicion of multigland disease (only included people with positive MIBI suggesting single gland disease)

Patient details:
n=52 solitary, n=1 double, n=3 hyperplasia
All first surgery</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
MIBI: performed in concordance with the Society for Nuclear Medicine’s procedure guideline for parathyroid scintigraphy. Subtraction scanning with 123I was combined with MIBI in some cases at the discretion of the nuclear radiologist.

Positive = not reported

Reference standard
Pathology and normocalcaemia (3 people not rendered normocalcaemic by first operation, but on a subsequent operation were found to have hyperplasia by histology and were rendered normocalcaemic (so final outcome known)).</td></tr>
<tr><td>2×2 table</td><td>MIBI</td><td></td><td></td><td>Total</td><td rowspan="3">Correctly localised single n=51 (TPs)
Incorrectly localised single n=1 (FNs)
Predicted single, final outcome double n=1 (FPs)
Predicted single, final outcome hyperplasia n=3 (FPs)</td></tr>
<tr><td></td><td>‘True positives’
51</td><td>‘False positives’
4</td><td></td></tr>
<tr><td></td><td>‘False negatives’
1</td><td>‘True negatives’
0</td><td></td></tr>
</table>

Reference	**Sprouse 2001[457]**				
	Total	52	4	56	
Statistical measures	Index text: 'Sensitivity': 98.1% 'Specificity': 0.0%				
Source of funding	Not reported*				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: sub selection of people suspected of having solitary adenoma				

Reference	**Stalberg 2006 [459]**
Study type	Retrospective study
Countries and setting	Australia, University Hospital
Study methodology	Data source: University of Sydney Endocrine Surgery Database Recruitment: consecutive patients with sporadic HPT undergoing MIP in the unit from June 2004 to October 2005
Number of patients	n = 100
Patient characteristics	Age, mean (range): 59.7 (22.4-85.8) years Gender (male to female ratio): 1:3 Ethnicity: not reported Inclusion criteria: sporadic PHPT and unequivocally single site of uptake on nuclear scan usingTc-99m-sestamibi on single photon emission tomography, who were undergoing MIP. PHPT defined as an inappropriate level of serum iPTH in the presence of hypercalcaemia without hypocalciuria Exclusion criteria: negative MIBI or MIBI indicating multiple sites of uptake (and undergoing standard bilateral exploration); any known hereditary HPT syndrome; secondary HPT; coincidental thyroid pathology; previous operation; lithium induced HPT. Details of imaging tests and surgical intervention: nuclear scan usingTc-99m-sestamibi on single photon emission tomography and focused US either by the radiologist pre-operatively or by the surgeon at operation, solely to guide incision placement. MIP undertaken using the lateral focused mini-incision technique. IOPTH was not used to guide decision making during the operation.

Reference	**Stalberg 2006** [459]
	Prior tests: sub selection of people with suspected single gland disease from MIBI results (people with negative MIBI and MIBI suggesting multiple sites excluded) Patient details: Previous operation excluded
Index test(s) and reference standard	Index test IOPTH: Immulite 2000 Intact PTH assay (DPC), a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay. Blood samples collected in EDTA plasma tubes. Positive = drop of 50% or more from the highest pre-incision or pre-excision value at 10 minutes Reference standard Normocalcaemia at 6 months follow-up. Unclear if all had histological confirmation but 98 patients had cure after removal of a single adenoma (so histology not necessary) and for the other 2 patients, histology is mentioned in results.
2×2 table	**IOPTH** / Reference standard + / Reference standard − / Total Index test + / 89 / 0 / 89 Index test − / 9 / 2 / 11 Total / 98 / 2 / 100 Delayed decrease seen in come people at 30 minutes (analysed as FNs here as 30 minute time point not included in review protocol). IOPTH results after excision of the first gland
Statistical measures	Index text: IOPTH Sensitivity: 90.8% Specificity: 100%
Source of funding	Not reported
Limitations	Risk of bias: none Indirectness: none (sub selection of people suspected of having solitary adenoma not a limitation for IOPTH index test)

Reference	**Stenner 2009**[464]
Study type	Retrospective study
Countries and setting	Italy, Hospital
Study methodology	Data source:

Reference	**Stenner 2009[464]**				
	Recruitment: series of patients with PHPT from March 2005 to March 2008 undergoing minimally invasive video-assisted parathyroidectomy (MIVAP)				
Number of patients	n = 13 (but one patient had MEN, excluded from IOPTH results here, n=12 sporadic PHPT)				
Patient characteristics	Age, median (range): 69 (33-86) years Gender (male to female ratio): 10:3 Ethnicity: not reported Inclusion criteria: PHPT (diagnosed on the basis of serum calcium, PTH and clinical symptom) undergoing MIVAP with pre-operative US, sestamibi and IOPTH. Eligible for MIVAP if had single adenoma <35mm on pre-operative imaging without associated goiter, suspected carcinoma of the thyroid, secondary or recurrent HPT, previous neck surgery and previous radiation to the neck. Exclusion criteria: not reported Details of imaging tests and surgical intervention: pre-operative US and sestamibi. Surgery was MIVAP with IOPTH. Prior tests: sub selection of people with single adenoma <35mm on pre-operative imaging. Patient details: n=12 solitary Recurrent HPT and previous neck surgery excluded				
Index test(s) and reference standard	Index test IOPTH: blood drawn before skin incision, PTH assay used was UniCel DxI 800 (Beckman Coulter, USA). Positive = drop >50% from pre-incision value at 10 minutes Reference standard Eucalcaemia for 6 months or longer. Final histology.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	Narrative comment that in one person without a >50% drop at 10 minutes, another sample was taken at 20 minutes and a >50% drop found (however, methods don't state that the 20 minute time point was routinely assessed if there was no drop at 10 minutes, therefore analysed as a FN (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute time point taken).
	Index test +	11	0	0	
	Index test −	1	0	0	
	Total	12	0	12	

Reference	Stenner 2009[464]
Statistical measures	Index text: IOPTH Sensitivity: 91.7% Specificity: -
Source of funding	Supported by Beckman Coulter grants (manufacturer of PTH assay)
Limitations	Risk of bias: none Indirectness: none (sub selection of people suspected of having solitary adenoma not a limitation for IOPTH index test)

Reference	Tampi 2014[476]
Study type	Prospective
Countries and setting	India, Hospital and research centre
Study methodology	Data source: n/a Recruitment: patients undergoing surgery for PHPT
Number of patients	n = 7
Patient characteristics	Age, range: 41-76 years Gender (male to female ratio): 3:4 Ethnicity: not reported Inclusion criteria: undergoing surgery for PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: not reported Prior tests: no preselection based on prior tests Patient details: n=7 solitary First surgery / re-operation not reported

Reference	**Tampi 2014[476]**			
Index test(s) and reference standard	Index test IOPTH: blood sample drawn from a peripheral vein. PTH levels were estimated by the use of a rapid Electrochemiluminescence immunoassay (ECLIA) on the Cobas 6000 combi analyzer. Positive = drop of >50% from baseline (unclear if pre-incision or pre-excision) at 10 minutes Index test Frozen Section (n=6): excised gland sent for frozen section examination Positive = not reported Reference standard Normalisation of post-operative calcium. Histopathological confirmation.			
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total
	Index test +	7	0	7
	Index test −	0	0	0
	Total	7	0	7
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: -			
2×2 table	**Frozen section**	Reference standard +	Reference standard −	Total
	Index test +	6	0	6
	Index test −	0	0	0
	Total	6	0	6
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: -			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	**Timm 2004[486]**
Study type	Prospective study
Countries and setting	Germany
Study methodology	Data source: n/a Recruitment: consecutive patients with PHPT referred to the clinic between November 2000 and February 2002
Number of patients	n = 40 (n=35 had IOPTH)
Patient characteristics	Age, median (range): 54 (20-74) years Gender (male to female ratio): 18:22 Ethnicity: not reported Inclusion criteria: biochemically proven PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: all patients had high resolution US and assessment of thyroid pathologies (endemic goiter region). Patients then had scintigraphy with SPECT. Open minimally invasive surgery (focusing on the 1 enlarged parathyroid gland) performed if identical localisation results by US and sestamibi and without thyroid pathology. Unilateral parathyroidectomy performed in people with a positive localisation study and concomitant multinodular thyroid pathology. Bilateral surgery performed in people with negative localisation studies, when an enlarged parathyroid could not be found at the described localisation or if IOPTH negative. Prior tests: no preselection based on prior tests Patient details: n=38 solitary, n=1 double, n=1 hyperplasia First surgery / re-operation not reported
Index test(s) and reference standard	Index test IOPTH: commercially available double antibody chemoluminescence quick PTH assay (Quick-Intraoperative Intact-PTH-Assay, Nichols Diagnostic Institute, USA). Pre-operative sample taken after intubation, prior to disinfection of the skin. Pre-excision drawn after identification of the suspected adenoma prior to resection. Positive = drop >50% from pre-operative or pre-excision levels at 10 minutes, if there was no drop at 10 minutes, samples were taken at

Reference	**Timm 2004[486]**				
	15 and 20 minutes. Reference standard Accuracy for prediction of further glands after excision of first gland (persistent hypercalcaemia or further glands identified). Definite histopathological findings.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	IOPTH results after excision of the first gland in people with multigland disease Note: method includes taking a 20 minute time point in people with a negative IOPTH at 10 minutes (can also calculate for only 10 minute time point – below)
	Index test +	33	0	33	
	Index test −	0	2	2	
	Total	33	2	35	
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	10 minute time point only
	Index test +	28	0	28	
	Index test −	5	2	5	
	Total	33	2	35	
Statistical measures	Index text: IOPTH (including 20 minute delayed timepoint in people without a fall at 10 minutes) Sensitivity: 100% Specificity: 100% Index text: IOPTH (10 minutes only) Sensitivity: 84.8% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	**van Ginhoven 2011[502]**
Study type	Retrospective study (also some prospective collection of data)
Countries and setting	The Netherlands, non-academic centre (department of surgery)
Study methodology	Data source: medical records Recruitment: all patients with biochemically proven PHPT scheduled to undergo surgery from August 2004 to September 2008

Reference	**van Ginhoven 2011[502]**
Number of patients	n = 50 (n=4 were excluded from the analysis as no definite outcome could be determined (n=2 not operated, n=2 not cured), therefore n=46)
Patient characteristics	Age, mean (range): 58 (20-82) years Gender (male to female ratio): 17:33 Ethnicity: not reported Inclusion criteria: biochemically proven PHPT, a pre-operative surgeon-performed US and scheduled to undergo surgery. Exclusion criteria: not reported Details of imaging tests and surgical intervention: all patients received preoperative localisation studies consisting of MIBI and/or US (radiologist and/or surgery-performed) and/or CT. both conventional exploration and MIP (operation of choice for suspected single gland disease) performed under general anaesthesia. IOPTH performed during MIP. Prior tests: no preselection based on prior tests Patient details: n=44 first operation, n=4 second operation.
Index test(s) and reference standard	Index test Surgeon-performed US: performed by one of the endocrine surgeons at the outpatient clinic (none were performed in the operating room prior to surgery). The linear ray probe with a frequency of 3-12MHz was used. When a possible enlargement of the parathyroid gland was identified, colour Doppler US was used to determine the vascularity of the lesion. Positive = adenomas defined as any oval, elongated or lobulated lesions connected with the thyroid during swallowing without a central hilum. Reference standard Perioperative surgical findings combined with an abnormal gland during pathological analysis and cure (normocalcaemic or hypocalcaemic with normal PTH levels). Uncured patients were left out of the analysis.
2×2 table	**Surgeon US** / Total: Correctly localised single n=37 (TPs) 'True positives' 37 / 'False positives' 2: Incorrectly localised single n=1 (FNs) Imaging negative, final outcome single n=5 (FNs) 'False negatives' / 'True negatives': Predicted single, final outcome multigland n=2 (FPs)

Reference	**van Ginhoven 2011[502]**				
		6	1		Correctly localised multigland n=1 (TNs)
	Total	43	3	46	
Statistical measures	Index text: Surgeon US 'Sensitivity': 86.0% 'Specificity': 33.3%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	**Vignali 2002[504]**
Study type	Retrospective study
Countries and setting	Italy, University Hospital
Study methodology	Data source: not reported Recruitment: consecutive patients with sporadic PHPT undergoing parathyroidectomy in the period from March 1997 to May 2001
Number of patients	n = 206
Patient characteristics	Age, mean (range): males 51, females 58 (21-82) years Gender (male to female ratio): 46:160 Ethnicity: not reported Inclusion criteria: sporadic PHPT (all had hypercalcaemia and elevated PTH) Exclusion criteria: not reported Details of imaging tests and surgical intervention: 130 patients, selected on the basis of preoperative imaging (neck ultrasound and/or 99mTc-sestamibi) indicating the presence of a single adenoma, absence of goitre, and no previous neck surgery, underwent minimally invasive video-assisted parathyroidectomy, and 76 underwent a standard cervical approach. Prior tests: no preselection based on prior tests

<table>
<tr><td>Reference</td><td colspan="5">Vignali 2002[504]</td></tr>
<tr><td></td><td colspan="5">Patient details:
First surgery / re-operation not reported</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
IOPTH: blood plasma samples drawn from a peripheral vein or occasionally from the internal jugular vein in EDTA tubes. PTH was measured by a quick immunochemiluminescent assay (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA).

Positive = drop >50% from the highest pre-incision (after induction of anaesthesia) or pre-excision (during manipulation of suspected adenoma) value at 10 minutes

Reference standard
Normocalcaemia at follow-up. In results, mentions pathological examination to confirm pathology in people whose IOPTH did not fall after excision of the first gland.</td></tr>
<tr><td>2×2 table</td><td>IOPTH</td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Narrative comment in results that one of the people with a FN had a delayed drop >50% at 20 minutes (however, methods don’t state that the 20 minute time point was routinely assessed if there was no drop at 10 minutes, therefore analysed as a FN (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute time point taken).

IOPTH results after excision of first gland in people with multigland disease (those who had a negative IOPTH and went on to either have further glands removed, or hypercalcaemia counted as TNs) (can calculate both).</td></tr>
<tr><td></td><td>Index test +</td><td>192</td><td>3</td><td>195</td></tr>
<tr><td></td><td>Index test −</td><td>2</td><td>9</td><td>11</td></tr>
<tr><td></td><td>Total</td><td>194</td><td>12</td><td>206</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text:
Sensitivity: 99.0%
Specificity: 75.0%</td></tr>
<tr><td>Source of funding</td><td colspan="5">University grants</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: none
Indirectness: none</td></tr>
</table>

Reference	**Wade 2012[508]**				
Study type	Retrospective study				
Countries and setting	USA, Medical College				
Study methodology	Data source: chart review of single institution Recruitment: patients with sporadic PHPT who underwent parathyroidectomy between December 1999 and December 2008				
Number of patients	n = 58 (study divides into 2 groups based on pre-operative ionised calcium, but all results combined in analysis here).				
Patient characteristics	Age, mean (range): elevated iCa 58; normal iCa 60 (25-86) years Gender (male to female ratio): 11:47 Ethnicity: not reported Inclusion criteria: sporadic, normocalcaemic PHPT (defined as normocalcaemic if they had no elevated serum calcium values during the 3 months prior to surgery). Exclusion criteria: persistent, recurrent, familial, secondary, or tertiary HPT Details of imaging tests and surgical intervention: Most of the patients underwent preoperative localization imaging (cervical ultrasonography (US), technetium-99m (99mTc)-labelled sestamibi scanning, or both). Prior tests: no preselection based on prior tests Patient details: n=50 single; n=9 multigland disease Persistent and recurrent HPT excluded				
Index test(s) and reference standard	Index test IOPTH: details reported elsewhere [533] Positive = drop by ≥50% from the highest baseline (either pre-incision or at time of parathyroid removal, time zero) value at 10 minutes (study also reports for a drop of 50% or more and into the normal range, not required by review protocol). Reference standard Normal serum calcium at last follow-up (all but 1 had normal serum calcium at last follow-up, but this person developed recurrent disease after 6 months, therefore none had persistent hypercalcaemia). Pathology.				
2×2 table	**IOPTH**	Reference standard +	Reference standard −	Total	Results of IOPTH after excision of all glands in

Reference	**Wade 2012[508]**				
	Index test +	55	0	51	people with multigland disease.
	Index test −	3	0	7	
	Total	58	0	58	
Statistical measures	Index text: Sensitivity: 94.8% Specificity: -				
Source of funding	No financial disclosures				
Limitations	Risk of bias: none Indirectness: none				

Reference	**Wei 1997[515]**
Study type	Prospective study
Countries and setting	Georgia, Medical College of Georgia Hospital
Study methodology	Data source: n/a Recruitment: consecutive patients with hypercalcaemia and a diagnosis of PHPT between December 1992 and January 1996
Number of patients	n = 22
Patient characteristics	Age, mean (range): 50.5 (22-76) years Gender (male to female ratio): 7:15 Ethnicity: not reported Inclusion criteria: hypercalcaemia and a diagnosis of sporadic PHPT (diagnosis confirmed by total and ionised calcium levels and intact PTH) Exclusion criteria: family history of HPT; prior neck surgery Details of imaging tests and surgical intervention: all patients underwent dual-phase Tc-99m-sestamibi scanning and bilateral exploration. The side of the neck where the adenoma was localised was explored first. An attempt was made to identify all parathyroid glands within the surgical field.

Reference	**Wei 1997[515]**				
	Prior tests: no preselection of the basis of prior tests Patient details: n=19 solitary (1 ectopic), n=3 hyperplasia. No prior parathyroid surgery				
Index test(s) and reference standard	Index test MIBI: dual-phase Tc-99m-sestamibi scanning using Tc-99m-sestamibi alone. A 1.5 hour delayed image followed by a 3 hour delayed scan and whole mediastinal view. 148MBq of Tc-99m-sestamibi administered intravenously and 15 2-minute images acquired with a gamma camera with a high resolution parallel hole collimator. The 2nd to 15th images were added together and the composite image normalised to the thyroid image Positive = scans interpreted by a single independent observer. Reference standard All patients had correction of hypercalcaemia (one required a second operation to confirm an ectopic adenoma) and pathology. Normal parathyroid glands biopsied and confirmed histologically.				
2×2 table	**MIBI**			Total	Correctly localised single n=16 (TPs) Incorrectly localised single n=2 (FNs) Imaging negative, final outcome single n=1 (FNs) Imaging negative, final outcome hyperplasia n=1 (TNs) Predicted single, final outcome hyperplasia n=2 (FPs)
		‘True positives’ 16	‘False positives’ 2		
		‘False negatives’ 3	‘True negatives’ 1		
	Total	19	3	22	
Statistical measures	Index text: MIBI ‘Sensitivity’: 84.2% ‘Specificity’: 33.3%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none				

Reference	**Witteveen 2011[524]**
Study type	Retrospective study

Reference	Witteveen 2011[524]
Countries and setting	The Netherlands, University Medical Centre
Study methodology	Data source: patients' hospital records Recruitment: control group with sporadic PHPT who had a scan before initial surgery
Number of patients	n = 42 (only able to calculate 2x2 table values for the first surgery subgroup (n=23). Not all patients undergoing re-operative surgery were cured, so final outcome unknown).
Patient characteristics	Age, mean (SD): first surgery (n=23) 59 (12) years Gender (male to female ratio): first surgery 2:21 Ethnicity: not reported Inclusion criteria: patients with persistent PHPT who had a scan before reoperative surgery or patients with sporadic PHPT due to single gland disease who had a scan before initial surgery (only initial surgery subgroup included in analysis in this review, n=23). Exclusion criteria: not reported Details of imaging tests and surgical intervention: SPECT following by bilateral, unilateral or MIP surgery. Bilateral neck exploration consisted of visualization of all four parathyroid glands. Unilateral neck exploration and minimally invasive neck exploration were guided by IOPTH. Prior tests: sub selection of people with single gland disease Patient details: n=19 solitary adenoma, n=4 single hyperplastic gland removed. First surgery n=23
Index test(s) and reference standard	Index test MIBI (SPECT): technetium 99m sestamibi single emission computed tomography (Tc99m-MIBI-SPECT). After IV injection of 500 MBq of Tc99m MIBI, planar images of the head and neck region and chest were performed. Scintigraphy was performed as a dual-phase single tracer examination. Images were acquired 15 min and 2 h after injection of the radiopharmaceutical. A gamma camera (Toshiba GCA-7200, Tokyo, Japan) equipped with low-energy high-resolution collimators was used for image acquisition. SPECT was performed 90 min after the injection. The filtered back projection was used for image reconstruction, using a Butterworth filter (8 order, subset 12). Positive = All Tc99m-MIBI-SPECT scans were reviewed by an experienced nuclear medicine physician who was blinded to the outcome

Reference	**Witteveen 2011[524]**				
	of the surgical procedure. Reference standard Cure (sustained normal serum calcium and PTH concentrations more than 6 months) and histological confirmation				
2×2 table	**MIBI (SPECT)**			Total	Correctly localised single n=14 (TPs) Incorrectly localised single n=1 (FNs) Imaging negative, final outcome single n=8 (FNs)
		'True positives' 14	'False positives' 0		
		'False negatives' 9	'True negatives' 0		
	Total	23	0	23	
Statistical measures	Index text: MIBI (SPECT) 'Sensitivity': 60.9% 'Specificity': -				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: sub selection of people with single gland disease				

Reference	**Ypsilantis 2010[537]**
Study type	Retrospective review
Countries and setting	UK, district general hospital
Study methodology	Data source: not reported Recruitment: consecutive patients with PHPT who underwent MIP with IOPTH at a district general hospital over 6 months
Number of patients	n = 11
Patient characteristics	Age, mean (range): 61 (46-67) years Gender (male to female ratio): 9:2 Ethnicity: not reported

<table>
<tr><td>Reference</td><td colspan="5">Ypsilantis 2010[537]</td></tr>
<tr><td></td><td colspan="5">Inclusion criteria: patients with PHPT who underwent MIP with IOPTH
Exclusion criteria: not reported

Details of imaging tests and surgical intervention: preoperative assessment with ultrasound and sestamibi scans then underwent MIP with IOPTH. However, 3 patients underwent planned full neck exploration facilitated by IOPTH.

Prior tests: no preselection based on prior tests

Patient details:
n=10 solitary, n=1 double
First surgery / re-operation not reported</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
<u>IOPTH:</u> intact PTH was assayed by a sandwich electrochemiluminescence immunoassay

Positive = drop ≥50% from baseline (immediately after excision, time zero) within 15 minutes (at 5, 10 or 15 minutes)

<u>Reference standard</u>
Post-operative normocalcaemia and histological confirmation.</td></tr>
<tr><td>2×2 table</td><td>IOPTH
Index test +
Index test −
Total</td><td>Reference standard +
10
0
10</td><td>Reference standard −
0
1
1</td><td>Total
10
1
11</td><td colspan="2">IOPTH results after excision of the first gland in people with multigland disease (i.e. TN if the person went on to have more abnormal glands located)</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text: IOPTH</u>
Sensitivity: 100%
Specificity: 100%</td></tr>
<tr><td>Source of funding</td><td colspan="5">Did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded
Indirectness: none</td></tr>
</table>

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

E.1 Imaging tests: test-and-treat

E.1.1 First operation

Figure 2: MIBI+US localisation: Normocalcaemia (6 months)

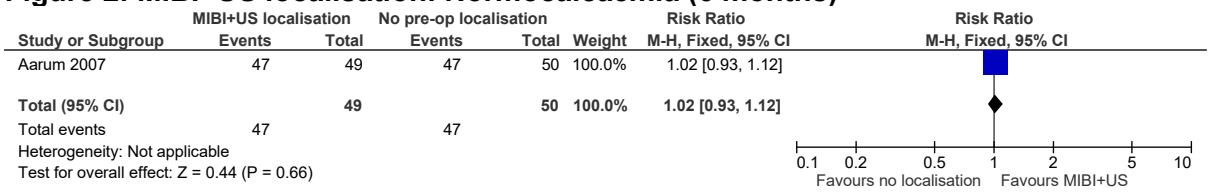


Figure 3: MIBI+US localisation: Adverse events (transient recurrent nerve paralysis)

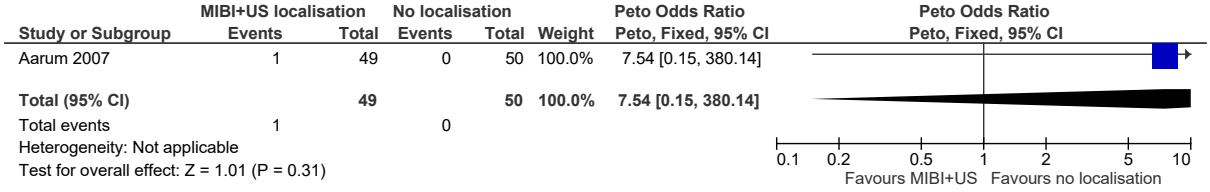
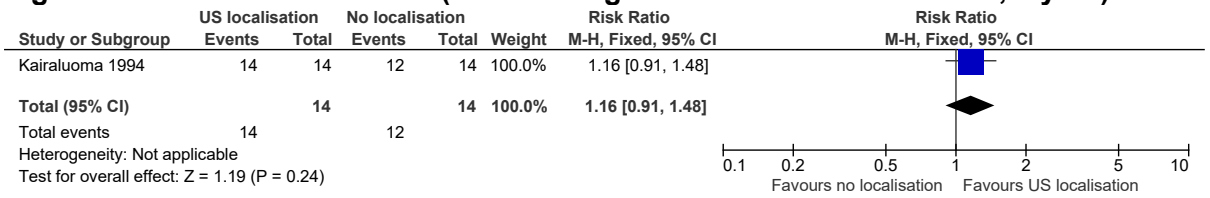
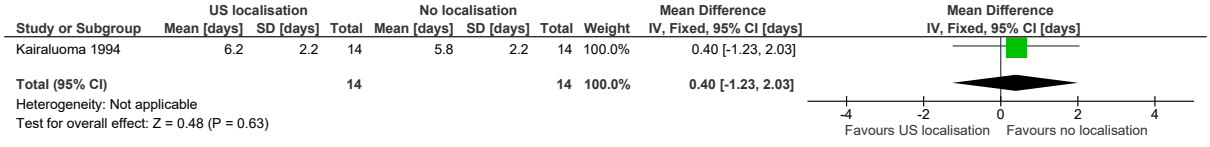


Figure 4: US localisation: Cure (no missed glands and normocalcaemia; 1 year)



Source: The failures had missed glands and hypercalcaemia – study notes that glands could not have been located using US in the 2 people not cured in the control group.

Figure 5: US localisation: length of hospital stay (days)



E.2 Imaging tests: diagnostic accuracy

E.2.1 First operation

Figure 6: US

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bradley 2016	41	2	6	0	0.87 [0.74, 0.95]	0.00 [0.00, 0.84]

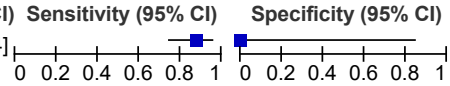


Figure 7: MIBI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonjer 1997	17	0	4	0	0.81 [0.58, 0.95]	Not estimable
Hindie 1998	21	1	6	2	0.78 [0.58, 0.91]	0.67 [0.09, 0.99]
Nilsen 2006	88	6	5	1	0.95 [0.88, 0.98]	0.14 [0.00, 0.58]
Orloff 2001	19	1	1	4	0.95 [0.75, 1.00]	0.80 [0.28, 0.99]
Saaristo 2002	13	0	3	4	0.81 [0.54, 0.96]	1.00 [0.40, 1.00]
Sprouse 2001	51	4	1	0	0.98 [0.90, 1.00]	0.00 [0.00, 0.60]
Wei 1997	16	2	3	1	0.84 [0.60, 0.97]	0.33 [0.01, 0.91]

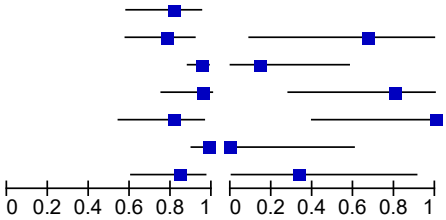


Figure 8: MIBI (subtraction)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Casas 1994	14	0	2	5	0.88 [0.62, 0.98]	1.00 [0.48, 1.00]
Hindie 1998	25	0	2	3	0.93 [0.76, 0.99]	1.00 [0.29, 1.00]
Kumar 2000	29	1	0	0	1.00 [0.88, 1.00]	0.00 [0.00, 0.97]

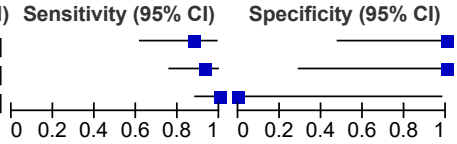


Figure 9: MIBI (SPECT)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nordin 2001	19	1	1	11	0.95 [0.75, 1.00]	0.92 [0.62, 1.00]
Ozkul 2015	10	0	0	1	1.00 [0.69, 1.00]	1.00 [0.03, 1.00]
Rubello 2006	22	0	0	0	1.00 [0.85, 1.00]	Not estimable
Witteveen 2011	14	0	9	0	0.61 [0.39, 0.80]	Not estimable

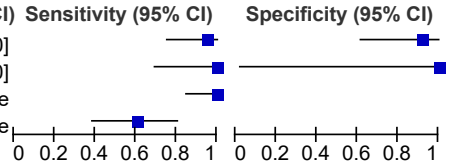


Figure 10: MIBI (SPECT/CT)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Harris 2008	16	2	2	3	0.89 [0.65, 0.99]	0.60 [0.15, 0.95]

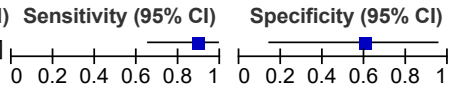


Figure 11: MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hamilton 1988	9	0	1	0	0.90 [0.55, 1.00]	Not estimable

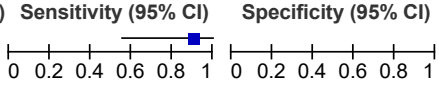
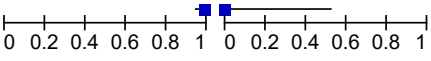


Figure 12: SPECT + US

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bobanga 2016	120	5	2	0	0.98 [0.94, 1.00]	0.00 [0.00, 0.52]



E.2.2 Mixed: first and re-operation

Figure 13: US

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jaskowiak 2002	32	2	18	5	0.64 [0.49, 0.77]	0.71 [0.29, 0.96]
Rossi 2000	7	0	4	0	0.64 [0.31, 0.89]	Not estimable
van Ginhoven 2011	37	2	6	1	0.86 [0.72, 0.95]	0.33 [0.01, 0.91]

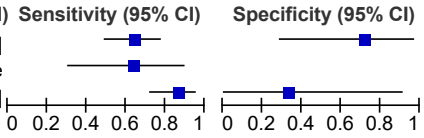


Figure 14: MIBI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jaskowiak 2002	38	3	12	4	0.76 [0.62, 0.87]	0.57 [0.18, 0.90]
Krausz 2006	33	0	1	2	0.97 [0.85, 1.00]	1.00 [0.16, 1.00]
Rossi 2000	7	0	4	0	0.64 [0.31, 0.89]	Not estimable

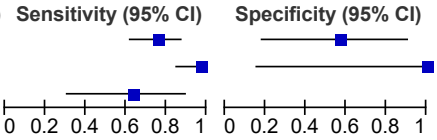


Figure 15: MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Rossi 2000	2	0	2	0	0.50 [0.07, 0.93]	Not estimable

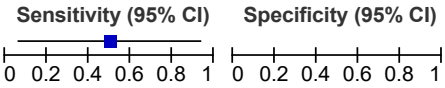
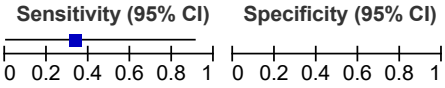


Figure 16: CT

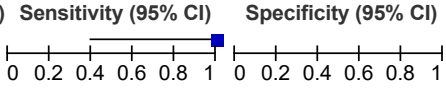
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Rossi 2000	1	0	2	0	0.33 [0.01, 0.91]	Not estimable



E.2.3 Re-operation

Figure 17: MIBI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bonjer 1997	4	0	0	0	1.00 [0.40, 1.00]	Not estimable



E.3 Intra-operative tests: test-and-treat

E.3.1 First operation

Figure 18: Normocalcaemia (6 months)

Study or Subgroup	IOPTH Events	IOPTH Total	no IOPTH Events	no IOPTH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Miccoli 2008	19	20	20	20	100.0%	0.95 [0.83, 1.09]
Total (95% CI)		**20**		**20**	**100.0%**	**0.95 [0.83, 1.09]**
Total events	19		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

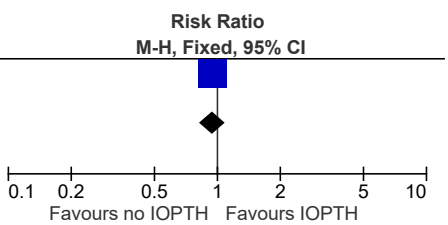
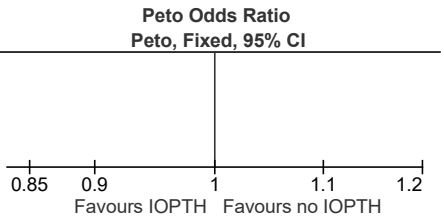


Figure 19: Post-operative complications

Study or Subgroup	IOPTH Events	IOPTH Total	no IOPTH Events	no IOPTH Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Miccoli 2008	0	20	0	20		Not estimable
Total (95% CI)		**20**		**20**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



E.4 Intra-operative tests: diagnostic accuracy

E.4.1 First operation

Figure 20: IOPTH (>50% drop at ≤10 minutes)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Agarwal 2012	55	0	3	1	0.95 [0.86, 0.99]	1.00 [0.03, 1.00]
Agha 2007	58	0	0	0	1.00 [0.94, 1.00]	Not estimable
Barczynski 2007	104	0	1	10	0.99 [0.95, 1.00]	1.00 [0.69, 1.00]
Chick 2017	75	0	3	1	0.96 [0.89, 0.99]	1.00 [0.03, 1.00]
Garner 1999	122	3	3	2	0.98 [0.93, 1.00]	0.40 [0.05, 0.85]
Hathaway 2013	291	2	9	1	0.97 [0.94, 0.99]	0.33 [0.01, 0.91]
Hwang 2010	247	1	19	13	0.93 [0.89, 0.96]	0.93 [0.66, 1.00]
Iacobone 2005	84	0	0	18	1.00 [0.96, 1.00]	1.00 [0.81, 1.00]
Kim 2015	51	0	0	2	1.00 [0.93, 1.00]	1.00 [0.16, 1.00]
Lee 2014	513	8	15	11	0.97 [0.95, 0.98]	0.58 [0.33, 0.80]
Lo 2003	62	0	4	0	0.94 [0.85, 0.98]	Not estimable
Lo 2007	93	0	5	2	0.95 [0.88, 0.98]	1.00 [0.16, 1.00]
Lombardi 2008	187	5	10	5	0.95 [0.91, 0.98]	0.50 [0.19, 0.81]
Mozzon 2004	242	1	12	8	0.95 [0.92, 0.98]	0.89 [0.52, 1.00]
Nilsen 2006	94	0	0	6	1.00 [0.96, 1.00]	1.00 [0.54, 1.00]
Patel 1998	32	0	0	1	1.00 [0.89, 1.00]	1.00 [0.03, 1.00]
Richards 2011	1533	50	62	105	0.96 [0.95, 0.97]	0.68 [0.60, 0.75]
Rossi 2000	8	0	0	0	1.00 [0.63, 1.00]	Not estimable
Rubello 2006	22	0	0	0	1.00 [0.85, 1.00]	Not estimable
Sagan 2010	26	0	0	7	1.00 [0.87, 1.00]	1.00 [0.59, 1.00]
Stalberg 2006	89	0	9	2	0.91 [0.83, 0.96]	1.00 [0.16, 1.00]
Stenner 2009	11	0	1	0	0.92 [0.62, 1.00]	Not estimable
Tampi 2014	7	0	0	0	1.00 [0.59, 1.00]	Not estimable
Timm 2004	28	0	5	2	0.85 [0.68, 0.95]	1.00 [0.16, 1.00]
Vignali 2002	192	3	2	9	0.99 [0.96, 1.00]	0.75 [0.43, 0.95]
Wade 2012	55	0	3	0	0.95 [0.86, 0.99]	Not estimable

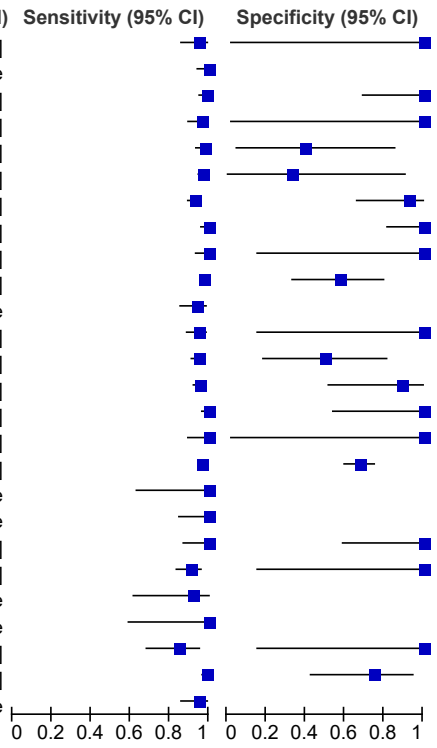


Figure 21: IOPTH (>50% drop at >10 minutes)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cayo 2009	146	0	9	6	0.94 [0.89, 0.97]	1.00 [0.54, 1.00]
Chen 2005	170	0	0	18	1.00 [0.98, 1.00]	1.00 [0.81, 1.00]
Hanif 2006	48	0	3	0	0.94 [0.84, 0.99]	Not estimable
Hughes 2011	193	14	7	14	0.96 [0.93, 0.99]	0.50 [0.31, 0.69]
Michel 2013	58	0	0	0	1.00 [0.94, 1.00]	Not estimable
Morks 2001	55	1	1	8	0.98 [0.90, 1.00]	0.89 [0.52, 1.00]
Ypsilantis 2010	10	0	0	1	1.00 [0.69, 1.00]	1.00 [0.03, 1.00]

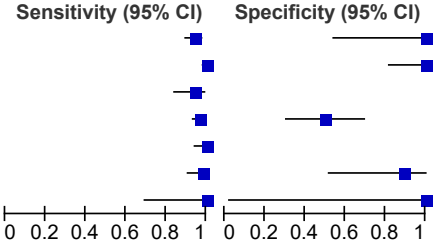


Figure 22: IOPTH (>50% drop at 10 minutes, plus 20 minute sample in people without a drop at 10 minutes)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barczynski 2007	105	0	0	10	1.00 [0.97, 1.00]	1.00 [0.69, 1.00]
Calo 2013	167	1	6	14	0.97 [0.93, 0.99]	0.93 [0.68, 1.00]
Chick 2017	78	0	0	1	1.00 [0.95, 1.00]	1.00 [0.03, 1.00]
Timm 2004	33	0	0	2	1.00 [0.89, 1.00]	1.00 [0.16, 1.00]

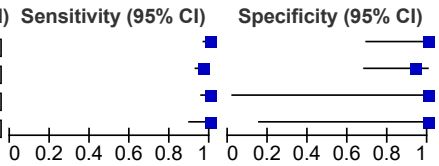
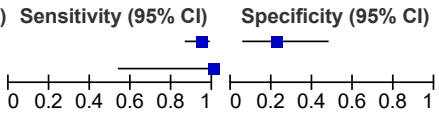


Figure 23: Frozen Sections

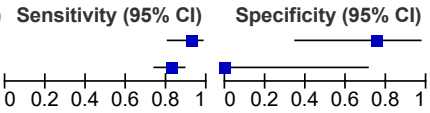
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Iacobone 2005	79	14	5	4	0.94 [0.87, 0.98]	0.22 [0.06, 0.48]
Tampi 2014	6	0	0	0	1.00 [0.54, 1.00]	Not estimable



E.4.2 Mixed: first and re-operation

Figure 24: IOPTH (>50% drop at ≤10 minutes)

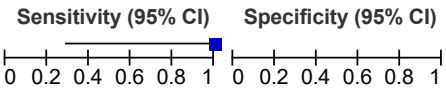
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jaskowiak 2002	45	2	4	6	0.92 [0.80, 0.98]	0.75 [0.35, 0.97]
Miura 2002	92	3	20	0	0.82 [0.74, 0.89]	0.00 [0.00, 0.71]



E.4.3 Re-operation only

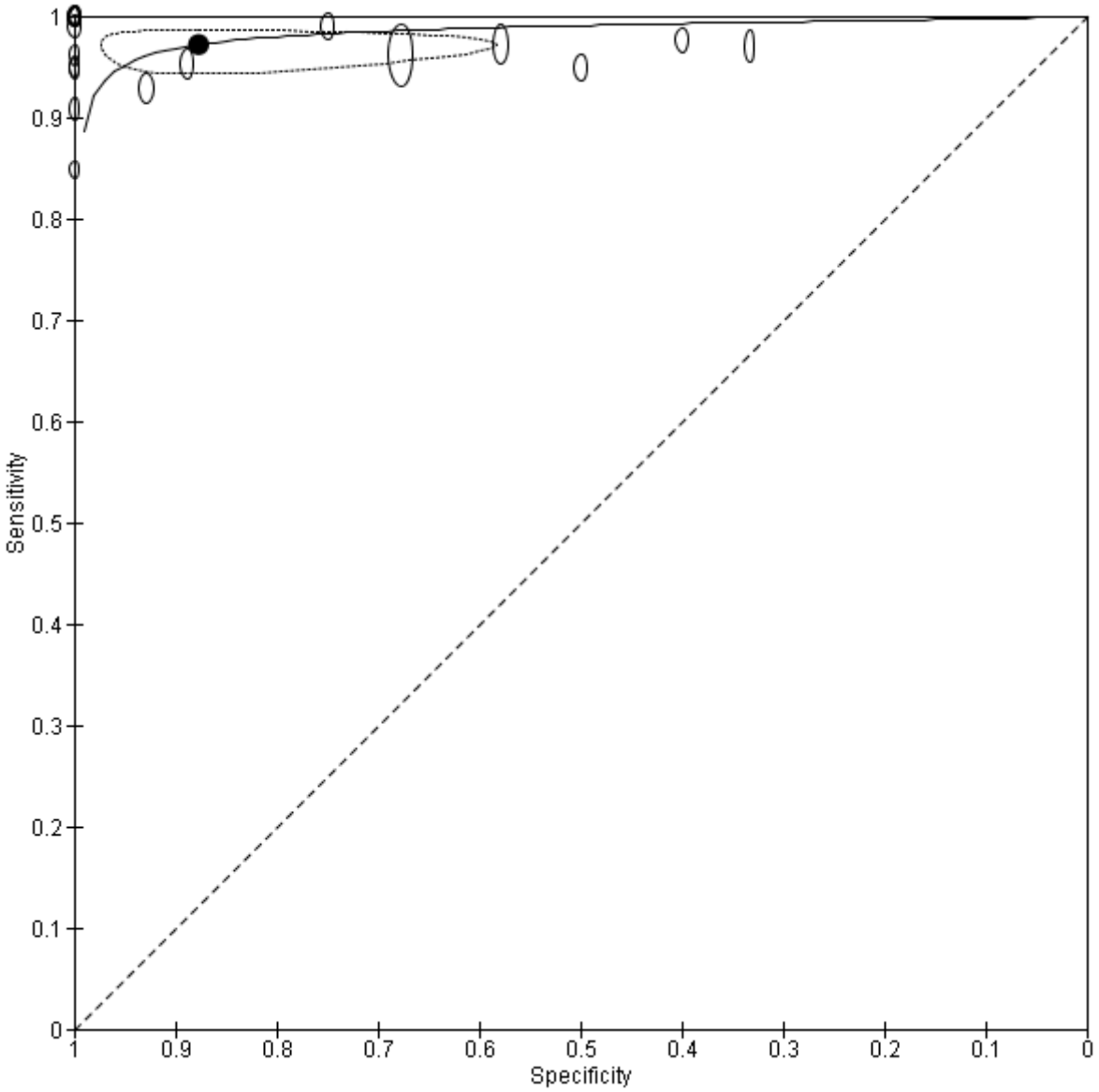
Figure 25: IOPTH (>50% drop at ≤10 minutes)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Rossi 2000	3	0	0	0	1.00 [0.29, 1.00]	Not estimable



E.5 ROC curves

Figure 26: IOPTH (>50% drop at ≤10 minutes). Pooled with prediction region (with study results by size)



Pooled analysis for IOPTH (>50% drop at ≤10 minutes) with prediction region. Filled circle (pooled sensitivity and specificity value), open circles (individual study point estimates with study results by size), dotted line (prediction region). For 7 of the 26 studies, specificity was not estimable and therefore unable to include in the meta-analysis. The meta-analysis was run twice (sensitivity analysis to check imputed values). Firstly for all 26 studies, with a value of 1 inserted in the TN cell for any studies with zero TNs. Secondly with these 7 studies excluded, only 19 studies included in the meta-analysis (for which specificity was estimable).The pooled sensitivity value was the same in both models. The specificity was 88.9% if all 26 studies were included and 86.8% if only the 19 studies with an estimable specificity were included (around a 2% over prediction of specificity by imputing values for TNs). Pooled specificity result presented here is for 19 included studies (7 studies with specificity not estimable excluded) as this is likely to give the best estimate of specificity.

Appendix F: GRADE tables

Table 23: Imaging test and treat (first operation stratum): MIBI+US pre-operative localisation versus no pre-operative localisation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-op MIBI and US versus no pre-op localisation	Control	Relative (95% CI)	Absolute		
Normocalcaemia (follow-up 6 months)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/49 (95.9%)	94%	RR 1.02 (0.93 to 1.12)	19 more per 1000 (from 66 fewer to 113 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events (follow-up 6 months; assessed with: transient recurrent nerve paralysis)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/49 (2%)	0%	Peto OR 7.54 (0.15 to 380.14)	20 more per 1000 (from 30 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT

[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.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs

Table 24: Imaging test and treat (first operation stratum): US pre-operative localisation versus no pre-operative localisation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-op US	No pre-op US	Relative (95% CI)	Absolute		
Cure (follow-up 1 years; assessed with: No missed glands and normocalcaemia[a])												
1	randomised	very	no serious	no serious	Serious[c]	none	14/14	85.7%	RR 1.16 (0.91	137 more per 1000 (from	⊕OOO	CRITICAL

	trials	serious[b]	inconsistency	indirectness			(100%)		to 1.48)	77 fewer to 411 more)	VERY LOW	
Length of hospital stay (days) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	very serious[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	14	14	-	MD 0.4 higher (1.23 lower to 2.03 higher)	⊕OOO VERY LOW	IMPORTANT

[a] Study notes that glands could not have been located using US in the 2 people not cured in the control group
[b] 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.
[c] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs

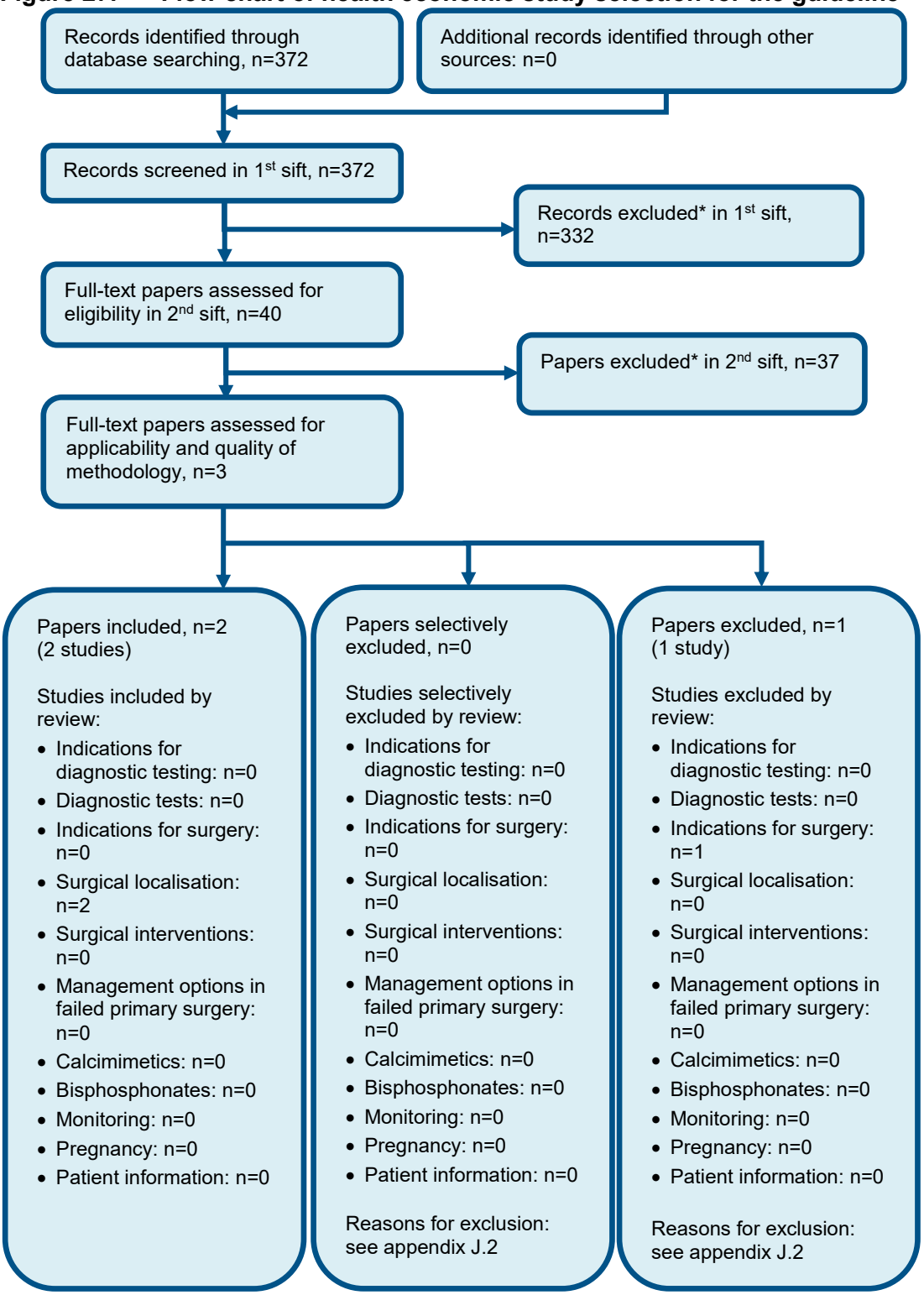
Table 25: Intra-operative test and treat (first operation stratum): IOPTH versus no IOPTH

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IOPTH**	**No IOPTH (to determine termination of surgery)**	**Relative (95% CI)**	**Absolute**		
Normocalcaemia (6 months) (follow-up 6 months)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/20 (95%)	100%	RR 0.95 (0.83 to 1.09)	50 fewer per 1000 (from 170 fewer to 90 more)	⊕⊕⊕O MODERATE	IMPORTANT
Post-operative complications (follow-up 6 months)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious imprecision	none	0/20 (0%)	0%	-	0 fewer per 1000 (from 90 fewer to 90 more)[b]	⊕OOO VERY LOW	IMPORTANT

[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.
[b] No events in either arm
c Downgraded by 1 increment if there was serious imprecision (sample size >70<350), and downgraded by 2 increments if there was very serious imprecision (sample size <70).

Appendix G: Health economic evidence selection

Figure 27: 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

Non-invasive preoperative imaging

Study	Pata G, Casella C, Magri GC, Lucchini S, Panarotto MB, Crea N et al. Financial and clinical implications of low-energy CT combined with 99m Technetium-sestamibi SPECT for primary hyperparathyroidism. Annals of Surgical Oncology. 2011; 18(9):2555-63			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CC **Study design:** Within-cohort study analysis. **Approach to analysis:** Analysis of individual level data for resource use (primarily diagnostic test costs and operating times associated with SPECT or SPECT/CT localisation). Unit costs applied. **Perspective:** Italian direct healthcare and medical costs. **Follow-up:** 6 months **Treatment effect duration:** n/a **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** People diagnosed with PHPT who underwent parathyroidectomy **Cohort settings:** N=55 Start age: 56 Male: 12 **Intervention 1:** SPECT followed by unilateral neck exploration on side suggested by imaging **Intervention 2:** SPECT/CT followed by unilateral neck exploration on side suggested by imaging	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1):cost saving of £91 (95% CI: £44 - £138; p=NR) **Currency & cost year:** 2009 Euros (presented here as 2009 UK pounds[(a)])] **Cost components incorporated:** equipment costs (including maintenance and depreciation), diagnostic costs (SPECT and SPECT/CT), surgical costs (calculated by duration of operation, using salary of 2 surgeons, an anaesthesiologist, 2 nurses and a nurse assistant; also includes cost of general anaesthesia), cost of postoperative care, cost of hospitalization.	None.	**ICER (Intervention 2 versus Intervention 1):** n/a **Analysis of uncertainty:** None undertaken.

Data sources
Health outcomes: None. **Cost sources:** Brescia Civic Hospital, Italy (data from one hospital).
Comments
Source of funding: NR. **Limitations:** Italian resource use (2004-2009) and unit costs (2009) data may not reflect current NHS context. QALYs not used as outcome measure. Analysis is based on a cohort study. Within-study analysis and so does not reflect full body of evidence. No exploration of uncertainty. **Other:** None
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: CC: comparative costing; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis;
(a) Converted using purchasing power parities[354]Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

Intra-operative techniques

Study	**Badii B, Staderini F, Foppa C, Tofani L, Skalamera I, Fiorenza G et al. Cost-benefit analysis of the intraoperative parathyroid hormone assay in primary hyperparathyroidism. Head and Neck. 2017; 39(2):241-246**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CC **Study design:** Within-cohort study analysis. **Approach to analysis:** Analysis of individual level data for resource use. Unit costs applied. **Perspective:** Italian university hospital **Follow-up:** 1 month **Treatment effect duration:** n/a	**Population:** Patients who underwent parathyroidectomy for primary hyperparathyroidism[(a)]. **Cohort settings:** N = 264 Age: 60 Male: 30% **Intervention 1:** No intraoperative PTH assay **Intervention 2:**	**Total costs (mean per patient):** Intervention 1: £581 Intervention 2: £1,218 Intervention 3: £681 Incremental (2−1): £637 (95% CI: NR; p=NR) Incremental (3-1): £100 (95% CI: NR; p=NR) Incremental (3-2): cost saving £537 (95% CI: NR; p=NR) **Cost breakdown:** Intervention cost:	None.	**ICER (Intervention 2 versus Intervention 1):** n/a **Analysis of uncertainty:** None undertaken.

Discounting: Costs: n/a; Outcomes: n/a	Rapid intraoperative PTH assay **Intervention 3:** Delayed intraoperative PTH assay – sample taken during surgery with results given postoperative day 1.	Int. 1: £0 Int. 2: £160 (5 assays) Int. 3: £23 (5 assays) Operating room costs: Int. 1: £563 Int. 2: £1,040 Int. 3: £563 Re-intervention cost: Int. 1: £1,127 Int. 2: £1,199 Int. 3: £0 **Currency & cost year:** 2015 (assumed) Euros (presented here as 2015 UK pounds[(b)]) **Cost components incorporated:** Rapid intraoperative PTH assay, delayed intraoperative PTH assay, operating room, cost of reoperation for surgical failures.		
Data sources				
Health outcomes: None. **Quality-of-life weights:** n/a. **Cost sources:** Not stated.				
Comments				
Source of funding: NR. **Limitations:** Italian resource use (2000 -2015) and unit costs (assumed 2015) data may not reflect current NHS context. QALYs not used as outcome measure. Analysis is based on a retrospective cohort study. Within-study analysis and so does not reflect full body of evidence. Cost sources not stated, nor cost year applied. No exploration of uncertainty. **Other:** None.				

Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: CC: comparative costing; 95% CI: 95% confidence interval;

(a) Preoperative localisation was based on MIBI, ultrasonography or both. Surgical approach was either minimally invasive video-assisted parathyroidectomy (incision<25mm), mini-incision parathyroidectomy (incision <35mm), or conventional parathyroidectomy (incision >35mm). Bilateral exploration mandatory when no concordance of preoperative imaging in locating adenoma, when intraoperative finding did not correspond to preoperative imaging, when ipsilateral gland to adenoma was hyperplastic or not in usual site.

(b) Converted using purchasing power parities[354]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Health economic analysis

I.1 Exploratory analysis for intraoperative parathyroid hormone testing during parathyroidectomy

I.1.1 Introduction

Intraoperative parathyroid hormone (IOPTH) testing is a relatively new technique that can be used during a parathyroidectomy. The test allows surgeons to determine whether or not the surgery has resulted in a cure while the patient is still in the operating theatre.

Following the clinical evidence review, the criterion for cure has been defined as a drop in parathyroid hormone levels 10 minutes post-excision of at least 50% from the baseline value. Where IOPTH levels do not drop by 50%, it indicates that the patient may have not been cured and surgeons have the option of continuing the surgery to search for further adenomas. If further tissue is identified and removed during the initial surgery, it can avoid the patient needing to be readmitted to hospital for a second operation. The advantage of IOPTH testing over laboratory-based PTH testing is that it can be conducted in the operating theatre, without the need for a sample to be sent to a central laboratory, thus reducing the waiting time for results.

The economic evidence review found one cost-comparison analysis relevant to this question. This study concluded that rapid IOPTH assay was the most costly option per patient, relative to both delayed (laboratory-based) PTH testing and no PTH testing during surgery. As the study was focused on cost comparisons only, no health-related quality of life outcomes were considered. The study also had a short follow-up period of 1 month, which may not sufficiently capture follow-up costs, and no sensitivity analysis was included. As well as this, the study was conducted in Italy, thus reported resource use and unit costs may not reflect the current NHS context. Hence, this evidence was assessed to not be sufficient to inform recommendations.

The guideline committee identified this area as a priority for original economic analysis as IOPTH is a high-cost intervention and is not routinely used in current practice. Hence, if IOPTH testing is to be recommended as part of parathyroid surgery, there is potential for a large impact on healthcare resources.

I.1.2 Methods

I.1.2.1 Overview

Having reviewed the clinical evidence for IOPTH testing, it was agreed by the committee that there was insufficient clinical data to populate a full economic model to assess the cost effectiveness of IOPTH during parathyroidectomy.

One test-and-treat study was identified in the clinical review. This paper suggested that using intraoperative testing during parathyroidectomy resulted in no clinical difference in surgical outcomes. However, committee consensus was that this study was not representative of the population in question due to methodological quality and small sample size.

Twenty-six diagnostic accuracy (first operation) studies were identified in the clinical review and were considered for the purpose of populating an economic model. However, little data was available to sufficiently populate patient pathways.

Due to the level of uncertainty surrounding model inputs, particularly due to lack of data for quality of life estimates, it was agreed that conducting a full cost-effectiveness analysis for IOPTH testing would require too many tenuous assumptions and results would be unreliable.

Consequently, it was decided that using an exploratory threshold approach would be more appropriate. Analysis was undertaken to answer two questions:

1. What is the improvement in the probability of successful surgery required to make testing with IOPTH cost-neutral?
2. What is the improvement in quality of life required to make testing with IOPTH cost-effective?

The first question was considered relevant as the cost of re-operation following a failed initial operation is high. Therefore, if IOPTH leads to a significant improvement in the success of first-time surgery, it is possible that the cost of the test would be offset by savings from avoided reoperation. The result from this analysis could then be considered by the committee and compared against real world data from the audit by the British Association of Endocrine and Thyroid Surgeons (BAETS), as well to that experienced by the committee members in practice, to gauge whether this degree of improvement is realistic. If so, it would be reasonable to conclude that IOPTH is cost effective as it would not incur any additional cost overall and improve health outcomes.

If the results from question one of the analysis suggest that IOPTH testing is unlikely to be cost neutral, its use may still be cost effective at the NICE £20,000 to £30,000 threshold. However, due to a lack of data for change in quality of life following successful parathyroid surgery, question two sought to determine what magnitude of improvement in QALYs would be necessary for IOPTH testing to be considered cost effective at the NICE threshold.

I.1.2.1.1 Comparators

The comparators included in the model are:

1. Parathyroidectomy with no IOPTH testing.
2. Parathyroidectomy with IOPTH testing.

I.1.2.1.2 Population

The population considered in this analysis are adults (18 years and over) with confirmed primary hyperparathyroidism caused by single adenoma, 4-gland hyperplasia, double adenoma or ectopic adenoma who are eligible for a parathyroidectomy. Patients who undergo parathyroidectomy for conditions other than PHPT are excluded as they are beyond the scope of this guideline.

I.1.2.1.3 Time horizon

The time horizon used for this analysis is one year. From committee discussions, this was considered a reasonable estimate for the length of time patients whose parathyroidectomy did not result in a cure would wait before a second surgery would take place. It is assumed that following a second surgery, all patients will be cured of PHPT, and therefore there is no difference in quality of life or on-going costs between these two treatment arms from that point onwards. (Please see section 1.8.2 for the rationale behind this assumption). Hence, the analysis has been limited to the period of time between first and second surgery, as this will be the only time where costs and quality of life – as measured by quality-adjusted life years (QALYs) – will be different between the two groups.

I.1.2.1.4 Perspective

This analysis was undertaken from an NHS and personal social services (PSS) perspective.

I.1.2.2 Approach to analysis

A decision-tree was used for this set of analyses (**Figure 28**) and includes the following data inputs:

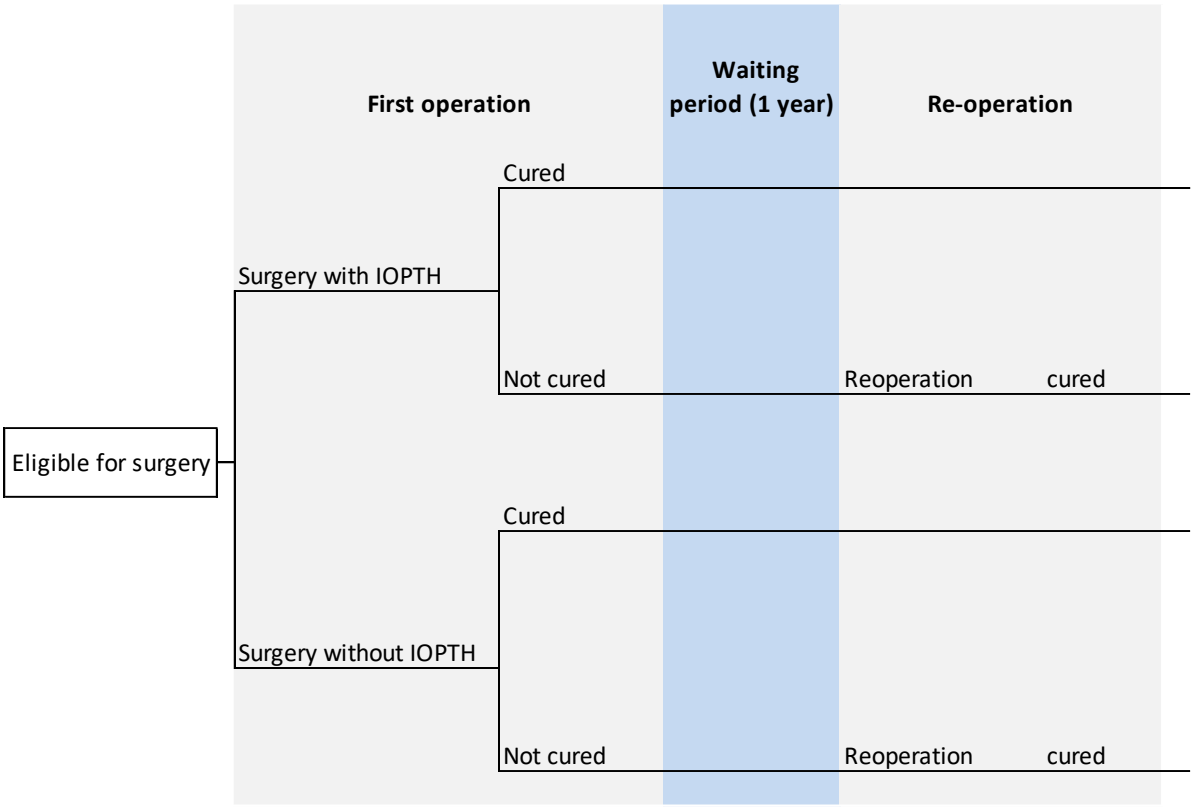
- Costs:
  - Surgical staff (surgeon, surgical assistant, anaesthetist, two nurses)
  - Operating theatre
  - IOPTH test equipment (machine)
  - IOPTH test reagents
  - Lab technician (to run IOPTH test)
  - Re-operation (including additional imaging and consultations)
- Resource use:
  - Surgery time
    - Additional surgery time for IOPTH test
    - Additional surgery time for conversion or extension
- Outcomes:
  - Probability of successful surgery with and without IOPTH
  - Probability of surgery being extended with and without IOPTH

I.1.2.2.1 Key assumptions

Due to the wide variation in current practice in the treatment of PHPT where surgery does not result in a cure, it was necessary for this analysis to make a number of assumptions with regard to the underlying patient characteristics:

- All patients entering the decision tree are undergoing parathyroid surgery for the first time.
- At the completion of the first operation, the patient is either cured or not cured.
- Patients who are cured will remained cured thereafter (i.e. do not have recurrent disease).
- Patients who are not cured after the first operation will undergo reoperation.
  - While it is possible that patients whose PHPT is not cured by initial surgery will not go on to have a second operation, there is very little clinical evidence or established clinical practice on the treatment for patients following unsuccessful surgery, therefore it would be difficult to estimate costs and quality of life for this group of patients. The committee agreed that the proportion of patients in this group is small, and therefore was considered negligible for the purpose of this analysis.
- For patients who undergo a second operation, there is a waiting period of one year between the first and second operations, as patients need to be reassessed before surgery is attempted again.
- Following reoperation, all patients are cured.
  - In practice, some patients will not be cured after reoperation. However, the committee discussed that the cure rates from second surgery are favourable with around 87% of patients being cured, according to the BAETs database. As the number of patients who remain not cured following second operation is very low, the committee agreed that it can be assumed to be negligible for the purpose of this analysis.
  - The key implication of this assumption is that, in both treatment pathways, the final outcome in both arms will be the same. That is, IOPTH testing will not change the ultimate number of patients who are cured once reoperation has been taken into consideration.

Figure 28: Decision Tree



I.1.2.2.2 Uncertainty

Given the lack of available data, a number of key inputs have been estimated by the committee. However, there remains a considerable degree of uncertainty due to variations in practice. Probabilistic sensitivity analysis was not deemed useful for this exploratory analysis. However, uncertainty was considered through multiple scenario sensitivity analyses.

For the base case, the input values chosen are those that have been deemed most likely to reflect real world practice, as advised by committee discussion. For sensitivity analysis, a number of scenarios will be considered that reflect the extremes of the range of estimates provided by the committee.

I.1.2.3 Model inputs

Only one test-and-treat study was identified during the clinical review that reported effectiveness – measured as the proportion of participants that achieved normocalcaemia at the 6-month follow-up after surgery – for IOPTH in surgical outcomes for PHPT. The study had a small sample size (n=40) and committee consensus was that the results are unlikely to be representative of the population in question, and that real-world data will provide a more accurate representation of clinical effectiveness. The committee advised that the 2017 National Audit[86] conducted by the British Association of Endocrine and Thyroid Surgeons (BAETS) would be the most suitable dataset for this analysis as it is more likely to reflect real-world outcomes of parathyroidectomy both with and without IOPTH testing[86]. This audit reports the surgical management of endocrine disorders in the UK over a 5-year period (between July 2010 and June 2015). Data is reported by members of BAETS and includes details of surgery and surgical outcomes such as short-term complications. In addition to this, the audit reports information on the use of pre-operative and intra-operative investigations and details of the pathology of the disease being treated.

It is important to note that while BAETS is a large data set – a total of 13,012 parathyroidectomies were recorded within a five year period – it has a number of limitations. Firstly, as the data is self-reported by health professionals, there is potential for bias as it is possible surgeons and practices with a higher success rate are more likely to report outcomes, thereby skewing cure rates higher. Secondly, the results are not adjusted for confounders, therefore it is not possible to establish whether the population included in the audit is representative of all people who have been assessed to be eligible for surgery. The committee discussed that in practice it is likely that IOPTH will be used in more complex cases, and therefore the results could also be skewed towards reporting higher cure rates as this is where IOPTH is most beneficial. In addition, the reported failure rates for IOPTH testing versus no IOPTH testing do not specify the type of surgery being performed nor the type(s) of pre-operative imagining used, hence it is important to note that the reported effectiveness cannot necessarily be attributed to IOPTH testing alone.

I.1.2.3.1 Effect of IOPTH testing on surgical outcomes

Probability of not being cured: the rate of failed parathyroid surgery – that is, where surgery does not result in a cure after first surgery – for both those who underwent parathyroidectomy with and without IOPTH were taken from the BAETS audit (2017).

Table 26: Probability of not being cured (persisting hypercalcaemia) following parathyroidectomy

	Probability	95% confidence interval
Parathyroidectomy without IOPTH	5.1%	4.6% - 5.7%
Parathyroidectomy with IOPTH	3.8%	3.0% - 4.8%

(a) Source: BAETS (2017)

Probability of surgery being extended: for patients undergoing planned targeted parathyroidectomy, there is a possibility they will be converted to 4-gland exploration if the surgeon considers it necessary and the surgery will be extended. Likewise, for patients undergoing planned 4-gland exploration, it is possible the surgery will extend beyond a typical length of time if the surgeon considers it necessary. The surgeon may make this decision with or without the use of IOPTH testing. To capture the increased cost of a negative test result, the BAETS audit was used. This reports that for patients undergoing planned targeted parathyroidectomy, 6.4% of surgeries without IOPTH testing converted to 4-gland exploration, while for surgeries with IOPTH testing, 12.0% were converted. For patients undergoing planned 4-gland exploration, no figures are available for the proportion whose surgery is extended. For the purpose of this analysis, it was assumed that the proportion of 4-gland explorations that are extended with and without IOPTH testing are the same as those for conversion in focused parathyroidectomies with and without IOPTH testing, respectively.

Table 27: Proportion of planned targeted parathyroidectomies that are converted

	Proportion
Parathyroidectomy without IOPTH	6.4%
Parathyroidectomy with IOPTH	12.0%

(a) BAETS (2017)[86]

The discrepancy between the increase in probability of extension and probability of surgical success suggest that a proportion of IOPTH tests will incorrectly show that the patient has not been cured even though in reality cure has been achieved (false negative test result). This represents an unnecessary extension of surgery and hence an inefficient allocation of healthcare resources. It was noted in committee discussion that the probability of unnecessary extension in 4-gland surgery is likely to be lower than that of unnecessary

conversion in targeted surgery; hence the above assumption may be an overestimate. This uncertainty will be addressed as part of the sensitivity analysis.

I.1.2.3.2 Resource use

Due to the lack of published data on the use of healthcare resources for parathyroid surgery, inputs to this model have largely been informed by committee discussion. This includes information regarding medical staff required for parathyroidectomy and the average length of time for surgery when IOPTH is used and when it is not.

First operation: the committee agreed for a typical operation, the medical staff required for a parathyroidectomy consist of a surgeon, a surgical assistant, an anaesthetist, and two surgical nurses. For surgery with IOPTH, there is also the added need for an IOPTH technician to be present to operate the machine.

The time required for an initial parathyroidectomy was estimated to be around 35 minutes on average, although the committee discussed that this is variable. Depending on individual circumstances, this may range between 25 to 60 minutes.

Additional time associated with IOPTH testing consists of the time required for the technician to run the test and any further operating time which may be required if the IOPTH test shows the patient has not been cured. The time for the test is considered to be standard at around 10 minutes. However, additional time for surgery that needs to be extended may range between 25 to 60 minutes. For the base case, an extension time of 35 minute was used as this was considered by the committee to reflect most 'typical' time for extension.

IOPTH testing: the IOPTH test requires the use of use of an analyser machine. The number of times the machine is used will determine the unit cost of the machine per person. The committee advised that the machine typically lasts around 6 years before it needs to be replaced. The number of times a machine is used will depend on how frequently the hospital performs parathyroidectomies. Hospitals that do not perform many parathyroidectomies a year may use it as few as 10 times per year. Hospitals that specialise in this area may use it up to around 132 times per year. As this varies widely between hospitals, it was not possible to place an exact value on the number of times a machine will be used. For the base-case, the committee estimated the machine will be used 20 times per year, as it was noted that most hospitals do not use IOPTH testing very frequently. The variation will be addressed as part of the sensitivity analysis.

I.1.2.3.3 Costs

Cost of first surgery: while NHS reference costs report standard costs for parathyroidectomy, these costs do not differentiate between surgeries that use IOPTH testing and those that do not. As this analysis is focused on the cost differences that result from IOPTH testing, the NHS reference cost was not used to cost initial surgery.

Instead, hourly costs of medical staff have been drawn from the PSSRU[108] and confirmed with the committee to ensure the correct cost category and job description has been selected for each staff member. The cost of an anaesthetist was not listed on the PSSRU, however the committee advised this is likely to be similar to that for a consultant surgeon, and therefore the same cost was assumed. An additional cost was included to account for the use of the operating theatre. The estimate has been taken from the analysis used in a previous NICE guideline (NG39)[334]. This consists of total costs associated with the use of an operating theatre less the costs paid to the staff.

These are then applied to the length of time required for surgery to determine the total cost difference between surgery with IOPTH testing and surgery without IOPTH testing.

Table 28: Cost of medical staff (per hour)

Input	Cost	Source
Surgeon (surgical consultant)	£ 107	PSSRU 2017[108]
Surgical assistant (foundation doctor FY2)	£ 30	
Anaesthetist[(a)]	£ 107	
Nurse (band 6)	£ 45	
Nurse (band 7)	£ 54	
IOPTH technician (band 4)	£ 31	
Operating theatre cost[(b)]	£ 201	NICE Major Trauma Guideline (NG39)[334]

(a) Not listed in PSSRU, committee advised using the cost of surgical consultant as proxy
(b) General theatre non-pay costs: costs other than pay to staff

Cost of IOPTH test: the cost of an IOPTH test consists of the cost of the machine (incorporated as an estimated cost-per-use), the reagent, and the additional staff cost of an IOPTH technician during surgery. As the cost of the machine and reagents are not publicly available, these were estimated by committee members with experience of using IOPTH. The value for the base case analysis has been taken as the mid-point of the range of costs provided. Variation in costs will be addressed as part of the sensitivity analysis.

Table 29: Cost of IOPTH test

Input	Data	Source
Analyser (machine)	£ 15,000	Committee estimate
Reagents (per pack)	£ 335	
IOPTH (band 4) technician	£ 31	PSSRU 2017[108]

Costs of failed surgery: the costs associated with failed surgery consist of that for reoperation, pre-operative imaging and consultations with a multidisciplinary team (MDT) responsible for treatment of the patient.

The unit costs for pre-operative imaging techniques were drawn from NHS Reference costs where available, and supplemented by committee estimates for items not included on the NHS Reference costs (**Table 30**).

The NHS Reference cost for an outpatient consultation with an endocrinologist has been used as the unit cost for pre-operative consultations (£158).

Due to the lack of a standardised set of costs that specifically apply to reoperation, for the purpose of this model we have used the NHS Reference cost for parathyroidectomy with a CC score of 2+ (£3417).

Variations in the pre-operative costs for a second surgery will be addressed as part of the sensitivity analysis.

Table 30: Pre-operative costs for re-operation for primary hyperparathyroidism

Type of imaging	Description	Cost
Ultrasound	Ultrasound Scan with duration of less than 20 minutes, without Contrast	£ 52
Sestamibi	Nuclear Medicine Parathyroid scan	£ 189
SPECT/CT	Parathyroid scan with SPECT/CT	£ 284
Parathyroid angiography and venous sampling		£ 1,320[(a)]

(a) Cost from a single NHS foundation trust

I.1.2.4 Sensitivity analyses

Due to the uncertainty of inputs, the robustness of results was examined using a series of scenario analyses to take into consideration variation in inputs. In the absence of published data to inform the range of values used for these analyses, estimates have been based on advice from the guideline committee.

I.1.2.4.1 One-way sensitivity analyses

The parameters subject to one-way sensitivity analyses and the ranges used are listed in **Table 31** below.

Table 31 Parameters subject to one-way sensitivity analyses

Input	Base case	Min	Max	Source
Analyser (machine)	£ 15,000	£ 0	£ 20,000	Committee estimate
Cost of reagents	£ 335	£ 270	£ 400	Committee estimate
Additional time for extended surgery (minutes)	35	20	60	Committee estimate
Cost following failed surgery				
Pre-operative costs for re-operation	£ 1,043[(a)]	£ 241[(b)]	£ 1,845[(c)]	NHS Reference costs
Cost of re-operation	£ 3,417	£ 2,103[(d)]	£4,755[(e)]	NHS Reference costs
Number of pre-operative consultations for re-operation	5	4	6	Committee estimate

(a) Average of minimum and maximum pre-operative costs, plus 3 MDT consultations
(b) Ultrasound and sestamibi, plus 4 MDT consultations
(c) Ultrasound, sestamibi, SPECT/CT and parathyroid angiography and venous sampling, plus 6 MDT consultations
(d) Day case
(e) Non-elective long-stay

Analyser (machine) upfront cost: as IOPTH testing is not currently used in most hospitals, the committee noted that the upfront cost of the machine itself may be prohibitive, especially for smaller healthcare providers which do not conduct many parathyroidectomies and expect to use the machine less frequently. At the same time, some larger hospitals which are more likely to use the technology may receive significant discounts from the manufacturers as they will benefit from on-going purchases of reagents used in each test. In some cases, it was suggested that the machine may be provided to the hospital at no cost. Hence, a minimum cost of £0 and a maximum of £20,000 were explored. The upper range here is the highest estimated cost given by the committee.

Cost of reagents: committee members who use – or have considered using – IOPTH testing advised that the price of reagents can vary depending on the number purchased, with lower unit prices for larger orders. This further reinforces the fact that where IOPTH testing is used more frequently they are more likely to be cost effective. Furthermore, while each packet of reagents may be used for multiple tests, once the packet is opened all tests must be used or discarded, hence if multiple operations can be undertaken at the same time, the cost of each test will again be lower. The committee advised that the price of reagents typically range between £270 and £400 per pack.

Additional time for extended surgery: in cases where surgery need to be extended, a longer time required for this extension potentially incurs greater costs as more healthcare resources are required to carry out the procedure. The committee advised that typical extension time is comparable to that of the initial surgery, therefore it has been assumed that this will range between a minimum of 20 and a maximum of 60 minutes.

Costs following failed surgery (including cost of pre-operative imaging and pre-operative consultations for re-operation and cost of re-operation): it was assumed that all patients whose initial surgery failed will undergo re-operation. It is also assumed that the cost of reoperation will be substantially higher than that of initial surgery, due to additional complications, the need for more advanced pre-operative imaging and additional consultations with the MDT prior to reoperation. It is expected that IOPTH is more likely to be cost-effective where costs associated with failed surgery is higher. For the purpose of this analysis, the minimum cost following failed surgery consist of the same pre-operative imaging as typical of an initial operation (ultrasound and sestamibi), and four consultations with an MDT; the maximum cost following failed surgery consists of two more advanced pre-operative imaging techniques (SPECT/CT and selective venous sampling) in addition to ultrasound and sestamibi, and six consultations with the MDT.

The relevant costs and level of resource use have been drawn from committee discussions.

I.1.2.4.2 Scenario analyses

In addition to the one-way analysis, a number of parameters are incorporated in the scenario analyses and are outlined in **Table 32** below. These scenarios have been designed using the upper and lower limits of the range of estimates for inputs – including those described for the one-way analysis above - outlined in the previous section.

Table 32 Parameters examined in scenario analysis

Input	Base case	Min	Max	Source
Number of times machine is used (per year)	20	10	132[(a)]	Committee estimate
Improvement in surgical success rate as a result of using IOPTH testing	1.3%	-0.2%	2.7%	BAETS (2017)

(a) Committee estimate of using the machine on 44 different days in one year, with an average of 3 times per day on the days it is in use.

Number of times machine is used: the committee discussed that where the rapid IOPTH analysers are used more frequently, the average cost associated with each test per person will be lower and thus more likely to be cost effective. Therefore, the committee considered it important to assess this in a sensitivity analysis. The committee advised that centres which do not frequently perform parathyroidectomies will use it as few as 10 times in one year, while larger centres with a speciality in parathyroidectomies may use it up to over 100 times a year. The upper limit used for analyses was taken from committee estimate that the machine will be used on 44 different days in one year, with an average of 3 times per day on the days it is being used. This is used along with the cost of the analyser machine (as described in the previous section) to calculate the cost per use for the machine.

Improvement in surgical success rate as a result of using IOPTH testing: the key objective of using IOPTH is to increase the probability of parathyroid surgery resulting in a cure. The BAETS audit reported the 95% confidence interval for these probabilities, and these have been included as part of the sensitivity analysis. The upper and lower confidence intervals reported in the BAETs audit were used to calculate the maximum and minimum level of improvement attributable to IOPTH testing. It should be noted that there is an overlap in the two confidence intervals; this indicates there is a level of uncertainty in the BAETS estimates regarding effectiveness of IOPTH testing during parathyroidectomy.

Table 33: Non-cure rate (persisting hypercalcaemia) following parathyroidectomy

	Base case	95% confidence interval
Parathyroidectomy without IOPTH	5.1%	4.6% - 5.7%
Parathyroidectomy with IOPTH	3.8%	3.0% - 4.8%

(a) Source: BAETS (2017)

Given that the lower boundary of non-cure rate for surgery without IOPTH testing is higher than the upper boundary of that for surgery with IOPTH testing, there is a possibility that parathyroidectomy without IOPTH testing could be more effective a achieving cure than parathyroidectomy with IOPTH testing.

As in the case of the one-way sensitivity analysis, relevant costs and level of resource use have been drawn from committee discussions.

I.1.2.4.2.1 Cost-neutrality analysis

1. *Minimum costs associated with IOPTH, maximum costs associated with failed surgery*

This scenario presents the setting that maximises the likelihood for IOPTH testing to be cost-neutral. This scenario was used to determine the minimum improvement in probability of surgical success required to make IOPTH testing cost neutral. The cost of IOPTH here have been chosen to reflect the lower end of what costs are likely to be in practice, and costs associated with failed surgery chosen to reflect the upper end of what they are likely to be in practice.

2. *Maximum costs associated with IOPTH, minimum costs associated with failed surgery*

By contrast, scenario B presents the setting to determine the maximum level of improvement in surgical success required to make IOPTH testing cost neutral.

I.1.2.4.2.2 Cost-effectiveness analysis

The required improvement in quality of life – given a certain cost setting – required to make IOPTH testing cost-effective will depend on the improvement in probability of curing PHPT through surgery as a result of using IOPTH testing. A larger improvement in this probability – and thus the larger number of additional number of people cured – means a smaller improvement in quality of life following successful surgery is required for IOPTH testing to be considered cost-effective.

The scenarios considered for cost-effectiveness are as follows:

3. *Minimum costs for IOPTH, maximum costs associated with failed surgery (as in scenario 1 above) with maximum improvement in surgical success rate*

Scenario 3 assumes the best-case scenario with respect to effectiveness of IOPTH testing in improving surgical success rate. In this scenario, the difference between the number of people cured after surgery with IOPTH testing and number of people cured after surgery without IOPTH testing is larger, hence the difference in total QALYs will be likewise be larger. Under this scenario, a smaller increase in quality of life per person would be required for IOPTH testing to be considered cost-effective.

4. *Minimum costs for IOPTH, maximum costs associated with failed surgery (as in scenario 1 above) with minimum improvement in surgical success rate*

Scenario 4 assumes the lowest possible rate of improvement in effectiveness of IOPTH testing. Consequently, a larger improvement in quality of life per person will be required for IOPTH testing to be considered cost-effective under this scenario.

As noted above, scenario 1 gives the most favourable outcome in terms of net costs from using IOPTH testing. Following this, scenarios 3 and 4 will consider the required improvement in quality of life for IOPTH testing to be cost-effective, given this cost setting.

5. *Maximum costs for IOPTH, minimum costs associated with failed surgery (as in scenario 2 above) with maximum improvement in surgical success rate*

6. *Maximum costs for IOPTH, minimum costs associated with failed surgery (as in scenario 2 above) with minimum improvement in surgical success rate*

Scenarios 5 and 6 use the same assumptions regarding improvements to probability of surgical success as 3 and 4 respectively. However, this will be considered under the cost assumptions of scenario 2, which assumes a higher net cost of IOPTH testing per person. Hence, the required improvement in quality of life following cure is expected to be higher in both scenarios compared to 1 and 2.

The result found in scenario 6 will represent the upper boundary of the required improvement in quality of life. That is, if it is reasonable to expect that curing PHPT will improve the patient's quality of life more than this result, then it would be feasible to conclude that IOPTH testing is a cost-effective intervention.

Table 34: Summary of scenarios 1 to 6

Scenario	Cost of IOPTH testing	Costs associated with failed surgery	Improvement in surgical success rate	Outcome
1	Min	Max	Outcome	Min. required improvement in surgical success rate
2	Max	Min	Outcome	Max. required improvement in surgical success rate
3	Min	Max	Max	Min. required improvement in QoL
4	Min	Max	Min	
5	Max	Min	Max	
6	Max	Min	Min	Max. required improvement in QoL

7. *Scenario analysis assuming 100% accuracy of IOPTH*

The exploratory cost-effectiveness analyses scenarios were re-run under the assumption of complete diagnostic accuracy for IOPTH tests. This scenario has been included as there is a high level of uncertainty regarding the diagnostic accuracy for IOPTH tests – in particular, with regard to the proportion of tests with a negative result (that is, showing the patient has not been cured) that are true negatives (that is, the patient actually has not been cured).

If the increase in proportion of surgeries that are extended for a parathyroidectomy with IOPTH testing relative to that of a parathyroidectomy without IOPTH testing is closer to the rate of improvement in surgical success, it indicates a lower rate of false positive results in IOPTH testing (i.e. where the test result shows non-cure for patients who are actually cured), thus lower unnecessary healthcare resource use. The committee advised that the increase in rate of extension in 4-gland surgery is likely to be lower than that of conversion in focused surgery, as surgeons who have conducted a full exploration are likely to have a better idea about the true nature of whether the patient has been cured. However, there is no clinical data comparing proportion of 4-gland explorations with IOPTH testing that are extended to that of 4-gland explorations without IOPTH testing that are extended. This scenario was incorporated into the model by assuming that the increase in the proportion of parathyroidectomies using IOPTH testing that are extended, relative to parathyroidectomies without IOPTH testing, is equal to the increase in proportion of patients cured for

parathyroidectomies using IOPTH testing relative to proportion of patients cured for parathyroidectomies without IOPTH testing. This latter figure is taken to be 1.3% as reported by BAETS.

As previously noted, if there are a high number of false negative results, there will be a high number of surgeries that are unnecessarily extended. The assumption of 100% diagnostic accuracy will then skew the results in favour of IOPTH tests being cost effective, as it implies there will not be any unnecessary extensions in surgeries using IOPTH tests.

Note this will only be used in the sensitivity analysis for cost effectiveness, not cost neutrality. This is because for cost neutrality, the improvement in probability of successful surgery is the result to be determined. Therefore, as the calculation of proportion of surgeries that are extended is dependent on this result, it cannot be a variable input for this calculation.

I.1.2.4.2.3 For both cost-neutrality analysis and cost-effectiveness analysis

8. Scenario analysis for non-rapid PTH test

An additional set of analyses was run to assess the cost effectiveness of a non-rapid IOPTH testing. The committee discussed that it is also possible (although uncommon) to test PTH during the operation, but not analyse the sample in theatre. In this case, the hospital does not need to acquire additional equipment, as the sample is sent to be analysed in the laboratory. The disadvantage of this method is that the turnaround time is much longer and consequently the surgical team and operating theatre would be required for a longer period of time as they wait for the results.

To assess the cost effectiveness of this scenario, the cost of running such a test was assumed to be the same as that of a standard PTH test, which has been estimated to be £8 using an average of quotes from 12 clinics, as reported by committee members. The time to run the test was extended to 30 minutes to reflect the average turnaround time for such a test.

I.1.2.5 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of the model calculations.

I.1.2.6 Calculations for cost-neutrality and cost-effectiveness

I.1.2.6.1 Cost-neutrality

In order for IOPTH testing during parathyroidectomy to be cost-neutral, the additional costs associated with conducting the test needs to be balanced out by future savings that are attributable to the use of the IOPTH test. That is, where IOPTH test improves the cure rate of parathyroidectomy, fewer patients will require a second operation and thus not incur the costs for this reoperation.

The cost of the initial parathyroidectomy is calculated by applying unit costs to length of time required for surgery. The BAETS data reports that a certain proportion of parathyroidectomies – both with and without IOPTH testing – will be converted or extended. If this occurs, there will be an additional cost.

The cost of surgery without IOPTH testing $C(A)$ has been calculated as the following weighted average:

$$C(A) = (C_1(A) \times P_1(A)) + (C_2(A) \times (P_2(A))$$

Where $C_1(A)$ is the cost of surgery without IOPTH testing that are not converted; $P_1(A)$ is the proportion of surgery without IOPTH testing that are not converted; $C_2(A)$ is the cost of surgery without IOPTH testing that are converted; and $P_2(A)$ is the proportion of surgery without IOPTH testing that are converted.

The same formula was used to calculate the cost of surgery with IOPTH testing $C(B)$.

Therefore, the incremental cost (C_{IOPTH}) of IOPTH testing compared to no IOPTH testing is given by:

$$C_{IOPTH} = C(A) - C(B)$$

Future cost savings ($C_{SAVINGS}$) attributable to using IOPTH testing is calculated by:

$$C_{SAVINGS} = (Improvement\ in\ cure\ rate) \times (Cost\ of\ reoperation)$$

IOPTH testing will be cost-neutral where $C_{IOPTH} = C_{SAVINGS}$. The aim of the analysis is to find the $improvement\ in\ cure\ rate$ required to achieve this cost neutrality.

I.1.2.6.2 Threshold analysis

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost effective if: • ICER < Threshold

The analysis will determine the QALY gain required for people undergoing parathyroid surgery with IOPTH testing compared to those without. Specifically, this refers to the additional QALYs gained from an increase in the number of patients cured after surgery due to the improvement in surgical success rate following IOPTH testing.

This difference then is: $QALYs(B) - QALYs(A)$, or the denominator of the right-hand side of the above equation, where B is surgery with IOPTH testing and A is surgery without IOPTH testing. Rearranging the above equation then gives:

$$\big(QALYs(B) - QALYs(A)\big) = \frac{Costs(B) - Costs(A)}{ICER}$$

An ICER threshold of £20,000 per QALY gained and £30,000 per QALY gained will be used in consideration of cost effectiveness. This exploratory analysis aimed to determine the minimum level of improvement in quality of life following a success operation required to make IOPTH testing cost-effective.

I.1.3 Results

I.1.3.1 Base case

Under the base case, results of the analysis showed that in order for IOPTH testing to be cost-neutral, there needs to be an improvement in the probability of surgical success of 11.3%.

Under the base case, results of the analysis suggest that in order for IOPTH to be cost-effective at the £20,000 threshold, an incremental QALY gain of 2.02 per additional person cured is required for each patient following successful parathyroid surgery. For the £30,000 threshold, a QALY gain of 1.35 per additional person cured is required.

I.1.3.2 Sensitivity analyses

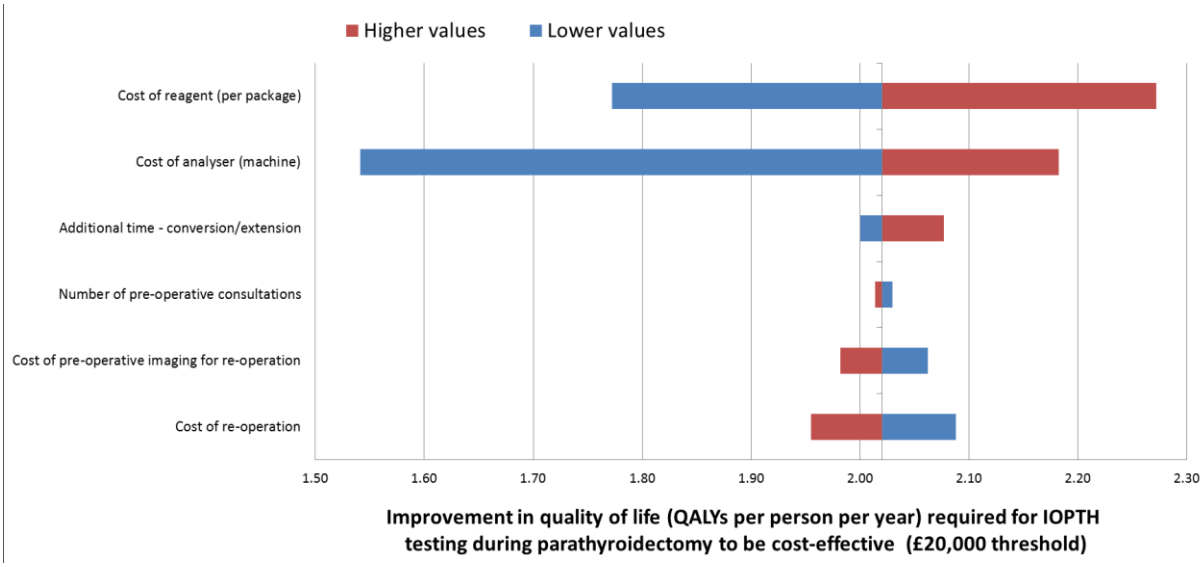
I.1.3.2.1 One-way sensitivity analyses

Results from one-way analysis (see **Table 35**) are illustrated in **Figure 29** below. It may be observed that the factors with the largest influence on outcomes are the cost of the analyser and the reagents. This was in line with expectations as these constitute the items subject to the greatest amount of variation. In the case where the analyser machine is provided at no cost, the required QALY gain for IOPTH testing to be cost effective is lowered to 1.54, all else being equal. Where the upper limit of £20,000 was assumed, this required gain increased to 2.18, all else being equal. For the reagents, the case where the lowest estimated value (£270) was assumed, the required QALY gain fell to 1.77, all else being equal. Under the scenario using the highest estimated value (£400), the required QALY gain increased to 2.27, all else being equal.

Table 35: Improvement in qualtiy of life following cure required for IOPTH testing during parathyroidectomy to be cost effective (£20,000 treshold)

	Lower boundary of estimates	Upper boundary of estimates
Cost of second operation	2.09	1.96
Cost of pre-operative imaging for re-operation	2.06	1.98
Number of pre-operative consultations	2.03	2.01
Additional time - conversion/extension	2.00	2.08
Cost of analyser (machine)	1.54	2.18
Cost of reagent (per package)	1.77	2.27

Figure 29 Improvement in quality of life following cure required for IOPTH testing during parathyroidectomy to be cost effective (£20,000 threshold)



I.1.3.2.2 Scenario analyses

IOPTH testing

Cost neutrality

Under scenario 1, the analysis shows that an improvement of 5.2% is required for IOPTH testing to be cost-neutral. Under scenario 2, an improvement of 30.0% is required for IOPTH testing to be cost-neutral.

Table 36: Improvement in probability of surgical success required for IOPTH testing during parathyroidectomy to be cost-neutral

Scenario	Improvement required
Base case	11.3%
Scenario 1	5.2%
Scenario 2	30.0%
Scenario 8	5.7%

Threshold analysis

Under scenario 3, an additional 0.35 QALYs for each additional person cured is required for IOPTH testing to be cost-effective at the £20,000 threshold, and an additional 0.23 QALYs at the £30,000 threshold.

For scenario 5, the required improvements are 1.51 QALYs for each additional person cured for IOPTH testing to be cost-effective at the £20,000 threshold, and an additional 1.01 QALYs at the £30,000 threshold.

Under scenarios 4 and 6, the use of IOPTH test during parathyroidectomy leads to a lower surgical success rate, hence this intervention is both less effective and more costly. In this case, the option of using IOPTH testing is dominated by the option of not using IOPTH testing.

Assumed 100% diagnostic accuracy

Under scenario 7, an additional 1.97 QALYs for each additional person cured is required for IOPTH testing to be cost-effective at the £20,000 threshold, and an additional 1.31 QALYs is required at the £30,000 threshold.

Non-rapid PTH testing

Under scenario 8, the savings in costs relating to the IOPTH equipment, reagents and IOPTH technician was partially offset by the additional costs incurred due to the longer turnaround time in testing.

Results of the analysis suggest that for non-rapid PTH testing to be cost neutral, there needs to be an increase in the probability of surgical success of 5.7%. For non-rapid PTH testing to be cost effective, the required incremental QALY gain per additional person cured is 0.88 at the £20,000 threshold, and 0.59 for the £30,000 threshold.

Table 37: Improvement in quality of life (QALYs) required for IOPTH testing during parathyroidectomy to be cost-effective

Scenario	£ 20,000 threshold	£ 30,000 threshold
Base case	2.02	1.35
Scenario 3	0.35	0.23
Scenario 4	Dominated	Dominated
Scenario 5	1.51	1.01
Scenario 6	Dominated	Dominated
Scenario 7	1.97	1.31
Scenario 8	0.88	0.59

I.1.4 Discussion

I.1.4.1 Summary of results

The result from the base case cost neutrality analysis shows that, even using highly 'favourable' assumptions, there needs to be an improvement in surgical success rate of 5.7% in order for IOPTH to be cost-neutral. Given that an average of 94.9% of parathyroidectomies without the use of IOPTH are successful in curing PHPT – as reported in BAETS – such an improvement would not be possible. Consequently, it is highly unlikely that use of IOPTH testing during parathyroidectomy is cost-neutral.

The results of the base-case threshold analysis suggests that there needs to be an improvement of 2.02 QALYs per additional person cured for IOPTH testing during parathyroidectomy to be considered cost-effective at the £20,000 per QALY threshold. That is, each patient who has been cured of PHPT following parathyroidectomy must experience an improvement of 2.02 QALYS per year, relative to their quality of life prior to surgery. As a year of full health is equivalent to 1 QALY, this improvement would not be possible. Hence, IOPTH testing is not cost effective.

The one-way sensitivity analysis showed that the inputs with the strongest influence on results for required QALY gains for IOPTH to be cost effective are the cost of the machine and the reagents.

Under sensitivity analysis using the most 'favourable' conditions for cost effectiveness (scenario 3), an improvement of 0.35 QALYs per additional person cured is required for IOPTH testing to be considered cost effective at the £20,000 threshold, and 0.23 QALYs per additional person cured at the £30,000 threshold. The committee advised that it was extremely unlikely that such an improvement in quality of life could be achieved from curing PHPT.

Under the assumption of the IOPTH test having 100% diagnostic accuracy, the required improvement in quality of life for IOPTH testing to be considered cost effective is slightly lower than the base case at 1.97 for the £20,000 threshold and 1.31 at the £30,000 threshold. However, this is still not a feasible improvement in quality of life for IOPTH testing to be cost effective.

The scenario analysis for a non-rapid IOPTH test indicated that an improvement in probability of surgical success of 5.7% is required for IOPTH testing to be cost neutral. A QALY gain of 0.88 per additional patient cured is required for IOPTH testing to be considered cost effective at the £20,000 threshold, and a QALY gain of 0.59 at the £30,000 threshold. As in the base case above, these outcomes have been considered highly unlikely to reflect reality and thus non-rapid IOPTH testing is also not cost neutral or cost effective.

I.1.4.2 Limitations

The purpose of the above analyses was to provide some indication as to whether using IOPTH testing during parathyroidectomy can be justified from an economic standpoint. Although the analyses sought to use the most appropriate methodology based on available evidence, the lack of clinical evidence remains a serious limitations that must be considered when interpreting model results.

Data input – effectiveness

Data for clinical effectiveness of IOPTH tests were largely taken from the BAETS audit data. The audit was considered to be the most comprehensive dataset on clinical outcomes available for parathyroidectomy and was considered to reflect the real world. However, there are a number of limitations for this data. First, all data in the audit have been self-reported by the surgeons. Hence, if there are any systematic differences in outcomes of surgeons who report outcomes and those who do not, the outcomes reported may be biased. For example, if surgeons who use IOPTH tests but have lower probability of surgical success are less likely to report outcomes, the increase in surgical success attributable to IOPTH testing may be overestimated, in which case IOPTH testing would be less cost-effective than indicated by results here. However, it is possible that surgeons with lower probability of surgical success with IOPTH tests will also have lower probability of success without IOPTH tests, therefore the overall impact of this on measurement of improvement attributable to IOPTH tests may be negligible. While it is not possible to determine from the available data whether either of these cases apply, committee consensus is that even if there is some bias in favour of the benefit of IOPTH testing to surgical outcomes, this is likely to be very small.

Another drawback of the BAETS data is that many of the reported outcomes which have been used as inputs to the model may not be directly applicable to the relevant population. The improvement in probability of successful surgery from using IOPTH testing has been calculated as the difference in the probability of successful surgery with IOPTH testing and that without IOPTH testing. However, it is unclear whether the population reporting these outcomes are identical. Therefore, if there are systematic differences between these two groups of patients it is possible that this observed difference may not be fully attributable to IOPTH testing. For example, if IOPTH is typically used for more complex cases, it is possible that it will achieve a smaller improvement in probability of surgical success than if it was used for the general population, in which case it will bias the results against IOPTH being cost effective. However, without more comprehensive data on underlying patient characteristics, it is not possible to conclude whether this is the case in practice.

Additionally, the outcomes for surgery with and without IOPTH were not reported separately for types of surgery (e.g. targeted surgery or 4-gland exploration). Therefore, as above, it is difficult to discern whether any difference in surgical outcomes is attributable to IOPTH testing or to differences in types of surgeries used. Again, this may bias the reported outcomes however it is not possible to tell from reported data the direction or magnitude of this bias.

Furthermore, while probability of conversion from planned targeted surgery to 4-gland exploration was reported separately for surgeries with IOPTH testing and surgeries without IOPTH testing, the probability of extending surgery in planned 4-gland exploration was not reported. For the purpose of analysis, it was assumed that the probability of conversion and probability of extension were the same. However, it was also noted in discussions with the committee that in the case of 4-gland exploration, it is less likely that a surgeon will choose to extend the surgery just on the basis of IOPTH testing, hence false positive results in IOPTH tests are likely to have less of an impact on probability of extension. The BAETS audit reports that 4-gland explorations are used in over half of all parathyroidectomies, hence it is possible the number of unnecessary extensions assumed for the above analyses has been overestimated. If this is the case, it is possible a smaller number of QALYs need to be gained per additional patient cured to make IOPTH testing cost effective. However, in consideration of above results, it is still highly unlikely that IOPTH testing will be cost effective, particularly due to the fact that even under scenario analysis with an assumption of 100% diagnostic accuracy, IOPTH testing remains not cost effective.

As well as this, there is uncertainty regarding whether IOPTH actually improves probability of success in parathyroidectomy. While on average there is an increase in probability of cure associated with the use of IOPTH testing, there is an overlap in the 95% confidence intervals for probability of cure with IOPTH testing and that for probability of cure without IOPTH testing. Hence, there is a possibility IOPTH tests do not improve outcomes, or even reduces probability of surgical success. If this is the case, IOPTH testing would not be cost-effective at any cost.

Data input – costs

Where possible, the analyses used NHS Reference costs and PSSRU unit costs to calculate cost inputs. However, due to the highly specialised nature of IOPTH tests, not all costs are listed on these sources. In particular, costs of IOPTH testing equipment are not publically available. Consequently, it was necessary for the input data to be supplemented with estimates drawn from committee experience. The uncertainty associated with these estimates is addressed by incorporating a large range for costs of both the analyser and the reagents. Given that neither extreme of the costs assumption altered the outcome by a significant degree, it is reasonable to conclude that the results are robust against variations on these costs.

Likewise, there is wide variation in the costs associated with re-operation, particularly in relation to pre-operative screening and consultations. This is due to the fact that re-operations typically have a higher level of complexity relative to initial operations, and there is no standardised approach. Sensitivity analysis shows that results are robust against these variations as overall conclusions regarding the cost effectiveness of IOPTH are not altered by either extreme of the range of costs considered.

In addition to this, potential long-term costs have not been included as part of this analysis. It has been noted above that if long-term costs of PHPT following non-cure from surgery is extremely high, then even a small improvement in the probability of surgical success as a result of using IOPTH may be sufficient for the intervention to be considered cost-effective. Following discussions with the committee, it was agreed that due to the high level of uncertainty regarding long-term care and outcomes of people with PHPT, it would not be possible to estimate such long term costs with any degree of accuracy. For example, while it would be feasible to calculate average cost of monitoring over a specific time period, it would be difficult to incorporate costs of events such as fragility fractures or cardiovascular events. As a result, the range for potential long-term costs was considered far too speculative and could not be taken without taking tenuous assumptions that are not be adequately supported by evidence. It is also noted that the relevant population for this outcome is extremely small, hence the likelihood of overall costs being affected is also quite low. Consequently, while

consideration for long-term costs should be noted, they have not been included as part of the main analysis.

Model assumptions

As noted in I.1.2.2.1, the assumption that all patients who are not cured by the first operation will go on to have reoperation and be cured is an oversimplification of real-world outcomes from parathyroidectomy. It is possible that a proportion of patients who are not cured the first time will choose not to have a second operation. It is also possible that some patients will not be cured even after re-operation. For these patients, the long-term treatment options are highly varied and are usually assessed on a case-by-case basis. Options may include further operations, pharmacological interventions such as calcimimetics, as well as long-term monitoring. As such, it was not possible to estimate long-term costs for these patients without making too many tenuous assumptions.

In interpreting the results of the analyses above, it must be noted that if IOPTH testing leads to a higher probability of cure in the initial operation, there will be fewer patients who face the probability of not being cured by parathyroidectomy – whether by choice not to have re-operation or due to unsuccessful re-operation – and who will need alternative long-term interventions, relative to the outcome where IOPTH testing is not used. If this is the case, there will be additional costs associated with parathyroidectomy without IOPTH, and a lower number of QALYs compared to the outcome where IOPTH testing is used. Hence, the above analyses may underestimate the cost-effectiveness of IOPTH if such long-term costs are very high.

In addition to this, the time horizon for this analysis has been limited to one year, which is assumed to be the average time between operations for patients who need reoperation. The committee advised this was a reasonable estimate for the average waiting time, however it was also noted that it was possible that a small number of patients will have a longer waiting time. Assuming IOPTH leads to higher probability of successful surgery, a longer waiting period would mean there will be a larger difference in QALYs for the group that had parathyroidectomy with IOPTH testing and those that had parathyroidectomy without IOPTH testing. A longer waiting period also means it is likely patients who are not cured during this time will accumulate higher treatment costs.

I.1.4.3 Implications of results

By designing scenarios to reflect the extreme values for cost and effectiveness inputs, the sensitivity analyses shows that while there will be some variation in the magnitude of results, none of the input settings lead to results that suggest IOPTH is likely to be either cost neutral or cost effective. However, while the results are relatively robust to variations in input values, the scenario analysis was unable to test for potential limitations imposed by the necessary simplifying assumptions in the above analyses.

As noted in the previous section, if it is found that in practice, treatment pathways and outcomes for parathyroidectomy to treat primary hyperparathyroidism is substantially different from those assumed in the model, it is possible that IOPTH is more likely to be cost effective than the modelling results suggest. At the same time however, it is also possible that IOPTH is less likely to be cost effective, if real-world settings are less ‘favourable’ than that assumed in the model – for example, if the improvement in probability of successful surgery attributable to IOPTH testing is smaller than assumed here. Without further evidence, however, it is not possible to determine which direction is more probable.

The model aimed to reflect real world outcomes as closely as possible, with underlying assumptions regarding treatment pathways determined following extensive committee discussion. It was agreed by the committee that, despite a substantial degree of variation in practice, the approach used in this analyses was – on average – an appropriate approximation. At the same time however, it was recognised that further research in areas

including the clinical effectiveness and diagnostic accuracy of IOPTH testing, long-term outcomes of non-cure following parathyroidectomy, and impact on quality of life following successful parathyroidectomy will be required in order to obtain improved certainty regarding the cost effectiveness of IOPTH testing during parathyroidectomy.

I.1.5 Conclusion

Under the assumptions of the model, this analysis suggests IOPTH testing is extremely unlikely to be cost-neutral. Likewise, results of the analyses suggest IOPTH testing is highly unlikely to be cost-effective. This is largely due the fact the probability of success for parathyroidectomy in curing primary hyperparathyroidism is very high to begin with, thus room for improvement is limited. At the same time, the magnitude of improvement attributable by IOPTH testing is highly uncertain, ranging from very small to possibly negative. It is also unclear from the available evidence whether any observable improvement is attributable to IOPTH testing or if it is influenced by other factors such as surgical skills. Hence, based on the results of this analysis, the addition of IOPTH testing during first-time parathyroidectomy is not considered cost-effective.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 38: Studies excluded from the clinical review

Reference	Reason for exclusion
Abboud 2007[2]	Unable to calculate 2x2 table values for protocol method.
Adler 2011[3]	Unable to calculate 2x2 table for either MIBI or US (for MIBI, number of correct scans only reported for 291/310 people who had either a negative scan or a single adenoma on scan; for US, only reported as the added benefit over MIBI)
Agha 2012[5]	Incorrect index test (contrast enhanced ultrasonography, and unable to calculate 2x2 table values for protocol method for other imaging tests). IOPTH incorrect criteria (only reports for >60% drop at 15 minutes, unclear if all people also had a >50% drop at 10 minutes).
Agha 2013[6]	Unable to calculate 2x2 table values for protocol method.
Ahmed 2013[8]	Incorrect reference standard (for IOPTH, unclear if histology also used as part of the reference standard or if only intraoperative findings and normocalcaemia).
Argiro, 2018 [24]	Incorrect study design for test and treat (comparing MRI, US and MIBI, but not randomised).
Akbaba 2012[9]	Unable to calculate 2x2 table values for protocol method.
Akin 2009[10]	Unable to calculate 2x2 table values for protocol method.
Al-Askari 2012[11]	Incorrect reference standard (unclear if normocalcaemia used as part of the reference standard and 6/204 had recurrent or persistent hypercalcaemia).
Alabdulkarim 2010[12]	Unable to calculate 2x2 table values for protocol method.
Albuja-Cruz 2013[13]	Unable to calculate 2x2 table values for protocol method. Sensitivity and specificity values provided for IOPTH but unclear how calculated from the numbers provided in the results.

Reference	Reason for exclusion
Alexandrides 2006[14]	Incorrect index test (people either had thallium-201/technetium-99m pertechnetate subtraction scan, 99mTc-tetrofosmin scan or 99mTc-sestamibi scan). Unable to calculate 2x2 table values for protocol method for US.
Alhefdhi 2011[16]	Incorrect reference standard (for IOPTH, unclear if histology also used as part of the reference standard or if only intraoperative findings and normocalcaemia).
Alhefdhi, 2017[15]	Incorrect reference standard-no histology
Aliyev 2014[17]	Incorrect reference standard (surgical findings).
Ammori 1998[18]	Unable to calculate 2x2 table for protocol method
Andersen, 2018 [19]	Incorrect study design for test and treat (comparing CT and MIBI SPECT/ CT, but not randomised).
Anderson 2008[20]	Unable to calculate 2x2 table values for protocol method (accuracy of MIBI for lateralisation not precise localisation).
Ansquer 2008[21]	Unable to calculate 2x2 table values for protocol method (accuracy calculated on a per-gland basis).
Apostolopoulos 1998[22]	Incorrect index test (99mTc-tetrofosmin)
Arciero 2004[23]	Incorrect reference standard (for IOPTH, no mention of histology used as part of the reference standard).
Arici 2001[25]	Unable to calculate 2x2 table values for protocol method.
Aspinall 2012[26]	Incorrect reference standard (normocalcaemia not part of the reference standard, assumption made that parathyroid glands left in situ were not pathologically enlarged or hyperfunctioning).
Attie 1988[27]	Unable to calculate 2x2 table values for protocol method
Bacher 2011[28]	Unable to calculate 2x2 table values for protocol method (accuracy for localisation to the correct side).
Badii 2016[29]	Unable to calculate 2x2 table values for protocol method (for pre-operative imaging or IOPTH).
Bambach 1978[30]	Incorrect population (recruited people with a diagnosis of primary or tertiary HPT and numbers included unclear).
Bandeira 2008[31]	No relevant outcomes (sensitivity, specificity or values for 2x2 table not provided). Incorrect reference standard (histology only).
Barber 2016[32]	Incorrect reference standard (IOPTH and pathology).
Barczynski 2006[33]	Unable to calculate 2x2 table values for protocol method
Barczynski 2009[36]	Incorrect index test (venous sampling test in isolation (not in conjunction with previous surgery results), for lateralisation and not precise localisation).
Barczynski 2009[35]	Incorrect reference standard (accuracy of IOPTH for prediction of normocalcaemia, but no pathological confirmation (states 'intraoperative frozen sections were performed only to confirm the parathyroid origin of the resected tissue)).
Barraclough 1981[37]	Incorrect index test (US imaging using a 5MHz frequency probe)
Beheshti, 2018 [38]	Incorrect study design for test and treat (no randomisation).

Reference	Reason for exclusion
Berczi 2002[39]	Sensitivity and specificity provided of MIBI and US for correct lateralisation but unable to calculate 2x2 values for protocol method.
Bergenfelz 1994[41]	Unable to calculate accuracy of IOPTH (study reports average decline in IOPTH at various timepoints, not the accuracy at a particular threshold).
Bergenfelz 1996[40]	Incorrect index test (accuracy of venous sampling test in isolation, for lateralisation and not precise localisation).
Bergenfelz 1997[44]	Incorrect reference standard (findings at neck exploration – although all people were rendered normocalcaemic, there is no mention of histological confirmation).
Bergenfelz 1998[42]	Unable to calculate 2x2 table values for IOPTH (sensitivity and specificity values provided in the paper but it is unclear if these refer to the whole study population or only people with single adenoma).
Bergenfelz 2009[45]	Unable to calculate 2x2 table values for protocol method (as not reported whether the people with negative imaging had a final outcome of single or multigland disease).
Bergenfelz 2007[43]	Unable to calculate 2x2 table values for protocol method
Bergenfelz 2011[46]	Not assessing accuracy of imaging or IOPTH
Bewick 2014[47]	Incorrect reference standard (unclear if normocalcaemia used as part of the reference standard)
Bhansali 2006[48]	Unable to calculate 2x2 table values for protocol method.
Bhatnagar 1998[49]	Incorrect reference standard (surgical resection and histopathology).
Biertho 2003[50]	Incorrect population (5% had carcinoma).
Bilezikian 1973[51]	Incorrect reference standard (not all people rendered normocalcaemic).
Billotey 1996[52]	Incorrect population (44% had secondary or tertiary HPT).
Bishop 2015[53]	Accuracy results only presented for different age subgroups and no overall accuracy reported.
Blower 1992[54]	Incorrect reference standard (no mention of normocalcaemia).
Boggs 1996[56]	Incorrect reference standard (for IOPTH, post-operative normocalcaemia reported but unclear if histology was used to confirm final outcome in all patients – only reported narratively in the results for some patients).
Borel Rinkes 2001[58]	Incorrect reference standard (post-operative normocalcaemia, but no histology).
Bradford Carter 1997[59]	Unable to calculate 2x2 table values for protocol method (classification of TPs from table 1 suggests accuracy for correct lateralisation of MIBI, not precise location).
Brennan 1981[61]	Incorrect population (unclear if only people with primary HPT included and 9% had FHH, suspected FHH or non-parathyroid hypercalcaemia).
Brown 2015[62]	Unable to calculate 2x2 table values for protocol method.

Reference	Reason for exclusion
Bugis 1995[63]	Unable to calculate 2x2 table values for protocol method.
Bumpous 2009[64]	Unable to calculate 2x2 table values for protocol method.
Burke 2013[65]	Unable to calculate sensitivity and specificity for correct gland localisation in the correct quadrant (scans were considered accurate if they localized an abnormal gland on the ipsilateral side of the gland removed at operation).
Butt 2015[66]	Incorrect reference standard (unclear if normocalcaemia used as part of the reference standard and 7% weren't rendered normocalcaemic).
Caixas 1997[67]	Incorrect population (Around 17% of the population had either secondary HPT or MEN).
Cakal 2012[68]	Incorrect reference standard (surgical and histopathological examination).
Calo 2012[71]	Overlap in the included participants with the Calo 2013[69] study (Calo 2013 study larger and therefore included in this review).
Calo 2013[70]	Unable to calculate 2x2 table values for IOPTH
Campbell 2015[72]	Unable to calculate 2x2 table values for protocol method (per-gland method used in study).
Carlier 2008[73]	Unable to calculate sensitivity and specificity values or 2x2 table for protocol method (per-gland method used in study).
Carnaille 1998[74]	Incorrect index test (pre-operative PTH, not IOPTH monitoring)
Carneiro 2003[77]	Incorrect reference standard (intraoperative findings and post-operative normocalcaemia, but no histology)
Carneiro-Pla 2006[76]	Incorrect reference standard (intraoperative findings and post-operative normocalcaemia, but no histology)
Carneiro-Pla [75]	Incorrect reference standard (intraoperative findings and post-operative normocalcaemia, but no histology)
Casara 2001[78]	Incorrect population (6% with MEN, parathyroid carcinoma or familial HPT). Incorrect reference standard (unclear if all patients had normocalcaemia following operation).
Casas 1993[80]	Unable to calculate sensitivity and specificity values or 2x2 table for protocol method
Catania 2002[81]	Unable to calculate 2x2 table values for IOPTH.
Catargi 1999[82]	Incorrect reference standard (operative findings/surgical exploration).
Caudle 2006[83]	Unable to calculate sensitivity and specificity values. Incorrect reference standard (calcium levels at 6 months only available in around 50% of people)
Caveny 2012[84]	Incorrect reference standard (histology and drop in IOPTH)
Cham 2015[87]	Unable to calculate sensitivity and specificity values or 2x2 tables
Chan 2005[88]	Conference Paper. Incorrect reference standard (histology)
Chapuis 1996[89]	Incorrect index test (IOPTH assay results weren't available until 2 hours after completion of surgery). Incorrect reference standard (surgical findings used as the reference standard for MIBI and US imaging).
Chatterton 1987[90]	Incorrect index test (Thallium-201-Technetium-99m subtraction scan).
Chen 1997[92]	Incorrect population (16% had secondary or tertiary HPT).

Reference	Reason for exclusion
Chen 2005[93]	Incorrect reference standard (intraoperative findings and post-operative normocalcaemia, but no histology)
Cheung 2012[95]	Incorrect reference standard (systematic review – normocalcaemia as part of the reference standard was not an inclusion criteria for studies)
Chiu 2006[97]	Agreement and comparison of different IOPTH criteria.
Cho 2014[98]	Incorrect population (6% had MEN)
Chou 1997[99]	Unable to calculate 2x2 table values for protocol method.
Chun 2013[100]	Incorrect reference standard (histology and decrease in PTH, no mention of cure/normocalcaemia).
Ciappuccini 2012[101]	Incorrect reference standard (surgical findings and pathology).
Civelek 2002[102]	Incorrect reference standard (histology).
Chazen 2012[91]	Incorrect reference standard (histology only, no normocalcaemia).
Clark 1984[103]	Incorrect population (11% had secondary HPT).
Clark 2003[104]	Unable to calculate 2x2 table values for protocol method (accuracy of MIBI for lateralisation, not precise localisation).
Cook 1998[105]	Incorrect population (38% had tertiary HPT). Incorrect reference standard (histology).
Cook 2010[106]	Incorrect population (subgroup of people who had an IOPTH rise at 5 minutes)
Cunha-Bezerra 2018 [107]	Incorrect study design for test and treat (comparing 4DCT, sestamibi and US, but not randomised).
Czerniak 1991[109]	Incorrect index test (dual radionucleotide parathyroid-radioiodinated toluidine blue / technetium 99m-thyroid scintigraphy). Unable to calculate 2x2 table values for protocol method.
D'Agostino 2013[111]	Incorrect reference standard. Reference standard was exploratory surgery or IOPTH drop (not normocalcaemia) – so in some people the reference standard for a negative gland was only IOPTH. “Glands were considered negative if they were either explored and deemed normal by the surgeon or not explored with drop in IOPTH that met the Miami criteria”
D'Agostino 2013[110]	Unable to calculate 2x2 values for protocol method (per-gland method used in the study).
Davis 2013[112]	Comparing different IOPTH criteria.
Day 2015[113]	Incorrect study design for test and treat (comparing 4DCT to no 4DCT, but not randomised). Incorrect reference standard (pathology and IOPTH).
De Simone[114]	Incorrect reference standard (unclear if all people rendered normocalcaemic).
Del Rio 2008[115]	Incorrect reference standard (histology). Unable to calculate 2x2 table values for protocol method.
Demirkurek 2003[116]	Unable to calculate 2x2 table values for protocol method.
Denham 1998[117]	Incorrect reference standard (systematic review – normocalcaemia as part of the reference standard was not an inclusion criteria for studies)
Derom 1993[120]	Incorrect population (includes people with secondary and tertiary HPT).
Derom 1994[119]	Article not in English
Deutmeyer 2011[121]	Unable to calculate 2x2 table values for protocol method.

Reference	Reason for exclusion
Dillavou 2000[122]	Unable to calculate 2x2 values for protocol method (accuracy of MIBI for lateralisation).
Doppman 1998[123]	Incorrect reference standard (some participants had angiographic ablation rather than surgery).
Drews 2003[124]	Incorrect population (50% of people had secondary HPT).
Dudek 1994[125]	Incorrect population (>75% secondary HPT). Incorrect index test (thallium-technetium scan).
Dunlop 1980[126]	Incorrect reference standard (histology)
Dwarakanathan 1986[127]	Incorrect reference standard (operative and pathological findings).
Dy 2012[128]	Incorrect index test (for IOPTH, accuracy only reported for a drop of 50% or more and to a normal or near-normal level – unable to calculate for a 50% drop alone)
Ebisuno 1997[129]	Incorrect reference standard (histology).
Eichhorn-Wharry 2011[130]	Incorrect reference standard (post-operative normocalcaemia not reported).
Eisenberg 1974[131]	Incorrect population (included people with secondary HPT).
Elaraj 2010[132]	Unable to calculate 2x2 values for protocol method.
Eloy 2006[133]	Incorrect index test (accuracy of venous sampling test in isolation, for lateralisation and not precise localisation).
Emmolo 2005[134]	Unable to calculate the accuracy of IOPTH.
Erdman 1989[135]	Incorrect reference standard (surgical findings).
Ersoy 2014[136]	Incorrect reference standard (states that all participants included in the analysis had biochemical improvement, unclear if this refers to all patients having normocalcaemia).
Estella 2003[137]	Incorrect population (8% MEN). Incorrect reference standard (not all people were rendered normocalcaemic)
Ezzat 2011[139]	Incorrect population (people with indication for total thyroidectomy)
Ezzat 2012[138]	Unable to calculate 2x2 values for protocol method.
Fayet 1997[140]	Incorrect reference standard (surgical and pathological findings)
Feingold 2000[141]	Unable to calculate 2x2 values for protocol method.
Fogelman 1984[142]	Incorrect reference standard (surgical exploration).
Foster 1989[143]	Incorrect index test (thallium-technetium subtraction scintigraphy). Incorrect reference standard (normocalcaemia not reported).
Frank 2017 [144]	Incorrect study design for test and treat (comparing 2D sonography, 3D sonography and sestamibi, but not randomised).
Freudenberg 2006[145]	Unable to calculate 2x2 values for protocol method (study uses per-gland method).
Gallacher 1993[146]	Unclear how sensitivity and specificity were calculated ('per-gland' or 'per-patient', and not enough information provided to complete 2x2 table)
Gallowitsch 1997[147]	Incorrect reference standard (histology in people who had surgery, not all people underwent surgery).
Gallowitsch 2000[148]	Incorrect reference standard (histology).
Garcia-Santos 2014[149]	Unable to calculate 2x2 table values for IOPTH and sensitivity or specificity not reported.
Garcia-Talavera 2010[152]	Incorrect reference standard (pathology and post-operative PTH, no mention of normocalcaemia)
Garcia-Talavera 2011[151]	Incorrect index test (accuracy of intra-operative gamma probe).
Garcia-Talavera 2016[150]	Unable to calculate 2x2 table values for protocol method.
Gauger 2001[154]	Only included people with double adenoma and assessed IOPTH

Reference	Reason for exclusion
	after excision of the first gland (therefore not possible to obtain true positive or false negative results).
Gawande 2006[155]	Unable to calculate 2x2 table values for protocol method.
Gedik 2017[156]	Unable to calculate 2x2 table values for protocol method.
Gergel 2014[157]	Unable to calculate 2x2 table for protocol method (study gives accuracy of US and MIBI for lateralisation and per-gland method).
Ghemigian 2015[158]	Unable to calculate 2x2 table values for protocol method.
Gil-Cardenas 2006[159]	Unable to calculate 2x2 table values for protocol method.
Gilat 2005[160]	Incorrect population (unclear age range of participants, one 13 year old included).
Gill 2011[161]	Incorrect reference standard (operative findings and histopathology).
Gimm 2012[162]	Incorrect index test (super-selective venous sampling: involved an initial conventional venous sampling, followed by a second round of additional samples taken from small venous branches in the region with the highest PTH level)
Giraldez-Rodriguez 2008[163]	Unable to calculate 2x2 table values for protocol (unclear if MIBI accurately localised in all cases, only states that it was positive or negative).
Glynn 2011[164]	Unable to calculate 2x2 table values for protocol method.
Gofrit 1997[165]	Unable to calculate 2x2 table values for protocol method.
Gogas 2003[166]	Unable to calculate 2x2 table values for protocol method (unclear if the two people with inaccurate pre-operative localisation would be classified as an incorrectly localised single adenoma by protocol method).
Goldstein 2006[167]	Incorrect reference standard (no mention of histopathology)
Gooding 1986[168]	Incorrect reference standard (surgical findings).
Grant 2005[169]	Incorrect population (people with familial HPT or MEN included).
Grayev 2012[170]	Provides sensitivity and PPV of MRI for lateralisation but unable to calculate 2x2 values for protocol method.
Griffith 2015[171]	Incorrect reference standard (surgical and pathological findings. Although all patients were cured, this could be based on normocalcaemia at 6 months or a 50% drop in IOPTH levels)
Gross 2004[172]	Incorrect population (14% had tertiary HPT).
Grosso 2007[173]	Unable to calculate 2x2 values for protocol method.
Guerin 2015[174]	Unable to calculate 2x2 values for protocol method (study uses ‘per-patient’ method to calculate sensitivity, but differs to protocol method).
Haber 2002[175]	Incorrect reference standard (biochemical cure could be based on IOPTH or normocalcaemia at 6 months, so not all people had confirmation of normocalcaemia).
Habibollahi 2018[176]	Incorrect reference standard (cure based on post-operative normocalcaemia or positive IOPTH).
Haciyanli 2003[177]	Incorrect population (10% of people had familial disease).
Halvorson 1994[178]	Incorrect reference standard (surgical, anatomical and pathological findings)
Hamamci 2011[179]	Paper not in English
Hamidi, 2018[180]	Incorrect study design for test and treat (no randomisation).
Hammonds 1976[182]	Not assessing the accuracy of imaging techniques for localisation.
Hanninen 2000[184]	Incorrect population (18% of people had secondary hyperparathyroidism).

Reference	Reason for exclusion
Hara 2007[185]	Incorrect population (79% of people in the study were receiving regular haemodialysis)
Hasselgren 1992[187]	Unable to calculate 2x2 table values for protocol method.
Hassler 2014[188]	Incorrect reference standard (surgery and histopathology, PTH measured after surgery to ensure cure). Unable to calculate 2x2 values for protocol method.
Hayakawa 2014[190]	Incorrect population (3/15 (20%) of people had MEN). Incorrect reference standard (histological confirmation without mention of normocalcaemia)
Heiba 2015[191]	Incorrect reference standard (histopathology).
Heineman 2015[192]	Incorrect reference standard (PTH levels used to determine cure, so elevated PTH in the setting of normocalcaemia could be considered as no cure).
Heizmann 2009[193]	Unable to calculate 2x2 table values for protocol method.
Heller 1993[194]	Incorrect reference standard (surgical findings without normocalcaemia)
Hewin 1997[195]	Unable to calculate 2x2 table values for protocol method (paper reports accuracy of US and MRI for lateralisation, not precise location)
Hiebert, 2018[196]	Incorrect study design for test and treat (comparing DECT, US and CT-MIBI, but not randomised).
Hindie 1995[199]	Incorrect reference standard (surgical findings and normocalcaemia without histology).
Hindie 1997[198]	Unable to calculate 2x2 table values for protocol method.
Hinson 2015[200]	Incorrect reference standard (normocalcaemia not reported)
Hjern 1975[201]	Incorrect reference standard (pathology, not all people rendered normocalcaemic).
Ho Shon 2001[202]	Unable to calculate 2x2 table values for protocol method.
Ho Shon 2008[203]	Incorrect reference standard (histopathology)
Hoda 2013[204]	Only included people with negative or inconclusive imaging (only 3 participants included).
Horanyi 2010[205]	Incorrect population (secondary hyperparathyroidism and MEN included). Incorrect index test (fine needle tissue aspirate).
Hornung 2011[206]	Incorrect index test (contrast enhanced ultrasonography). Unable to calculate 2x2 values for protocol method for conventional US).
Hunter 2012[208]	Incorrect reference standard (histology alone, no mention of cure/normocalcaemia). Histology alone used to confirm presence of adenoma in a region identified on the scan. Unclear how absence of adenomas in all other glands was confirmed (suggested that surgeries were focused or unilateral and no mention of cure/normocalcaemia)
Ibrahim 2015[212]	Incorrect reference standard (brief statement in abstract 'surgical findings and results of clinical follow-up as a reference standard', but no details provided in methods, unclear if normocalcaemia was used).
Ibraheem 2018[211]	Review. Screened for relevant references
Ikuno 2018[213]	Incorrect reference standard-no histology
Inabnet 1999[214]	Unable to calculate sensitivity and specificity or 2x2 values. Incorrect index test (IOPTH assay taken at 30, 60, 90 and 120 minutes after excision (our protocol specifies 5, 10 or 20 minutes)
Irvin 1993[215]	Incorrect reference standard (IOPTH prediction of post-operative

Reference	Reason for exclusion
	normocalcaemia, but no histology)
Irvin 1994[216]	Incorrect reference standard (normocalcaemia not reported for all included participants).
Isidori 2017[217]	Incorrect reference standard (histology).
Ito 2007[218]	Incorrect index test (accuracy of venous sampling test in isolation, for lateralisation and not precise localisation).
Itoh 2003[219]	Incorrect population (secondary hyperparathyroidism)
Jabiev 2009[220]	Unable to calculate 2x2 table values for protocol method
James 2014[221]	Incorrect population (used tissue from patients undergoing surgery for thyroid or parathyroid disease)
Jarhult 1985[222]	Incorrect reference standard (histology).
Jaskowiak 1996[223]	Unclear if accuracy measures are calculated against a reference standard using normocalcaemia.
Javaid 1999[225]	Incorrect reference standard (histology).
Johnson 2001[226]	Incorrect population (also included people with MEN, renal failure and carcinoma)
Johnson 2010[227]	Incorrect population (1 participant out of 15 had MEN). Unable to calculate 2x2 table values for protocol method
Johnston 1996[228]	Unable to calculate 2x2 table values for protocol method (unclear if those not cured had a final diagnosis of single or multi-gland disease).
Joliat 2015[229]	Incorrect reference standard (unclear if normocalcaemia measured as part of the reference standard)
Jones 2001[231]	Unable to calculate 2x2 table values for protocol method.
Jones 2002[230]	Incorrect population (23% of people had secondary HPT, parathyroid cancer, parathyromatosis or MEN).
Jorna 2007[232]	Unable to calculate 2x2 table values for protocol method.
Kairaluoma 1993[235]	Incorrect population (10% had familial hyperparathyroidism or MEN). Incorrect reference standard (intraoperative findings).
Kairaluoma 1994[233]	Incorrect population (27% of people had MEN).
Kairys 2006[236]	Unable to calculate 2x2 table values for protocol method.
Kandil 2012[237]	Incorrect reference standard (normocalcaemia not mentioned)
Kang 1993[238]	Incorrect reference standard (surgical reports)
Karakas 2012[239]	Incorrect reference standard (states surgical cure was achieved in all patients, but unclear if this was defined by normocalcaemia or a positive IOPTH decline).
Katayama 1990[240]	Paper not in English
Kaur 2016[241]	Incorrect reference standard (normocalcaemia not mentioned)
Keane 2013[242]	Incorrect reference standard (histological confirmation used to confirm the true location of the adenoma, post-operative PTH or calcium returning to normal used to confirm the true location if histology inconclusive). Unable to calculate 2x2 table.
Kebapci 2004[243]	Unable to calculate 2x2 table for protocol method.
Keidar 2017[244]	Incorrect reference standard (states intra-op and post-op biochemical workup as well as surgical findings and histopathological results, but unclear if post-op normocalcaemia used). Gives number of adenomas with same Perrier localisation on imaging and surgery, but unable to calculate 2x2 table.
Kelly 2014[245]	Incorrect reference standard (pathological findings used as the reference standard without normocalcaemia)
Khaliq 2003[246]	Unable to calculate 2x2 table values for protocol method.

Reference	Reason for exclusion
Khan 1994[247]	Incorrect population (type of HPT not reported and unclear if any people had MEN or familial HPT).
Khan 2015[248]	No relevant outcomes (diagnostic accuracy not reported)
Khorasani 2014[249]	Incorrect reference standard (histopathology)
Kim 2012[252]	Incorrect reference standard (lesions confirmed pathologically only)
Kim 2016[251]	Unable to calculate 2x2 table values for protocol method.
Klieger 1998[253]	Incorrect population (31% had a history of chronic renal failure)
Kluijfhout 2016[255]	Unable to calculate 2x2 table values for protocol method (per-gland accuracy reported).
Kluijfhout 2017[254]	Systematic review (unable to calculate 2x2 table values for protocol method).
Kobayashi 1998[256]	Accuracy of individual preoperative imaging tests not assessed.
Koberstein 2016[257]	Incorrect reference standard (intraoperative findings)
Koksal 2006[258]	Unable to calculate 2x2 table values for protocol method (not enough detail provided to determine if imaging is accurately localising to the precise location, or to side of adenoma).
Koong 1998[259]	Incorrect reference standard (surgical findings and histology only). Unable to calculate 2x2 values for protocol method.
Koren 2005[260]	Unable to calculate 2x2 table values for protocol method.
Kovatcheva 2014[261]	No diagnostic accuracy measures for localisation (assessing US-guided high-intensity focused ultrasound as a non-invasive treatment for PHPT).
Koyuncu 2005[262]	Incorrect reference standard (histology only) Histology used to confirm presence of abnormal gland and if no adenoma was found then other glands were explored. But if an abnormal gland was located first time, there was no use of cure/normocalcaemia to confirm no other abnormal glands.
Krakauer 2016[263]	Unable to calculate 2x2 values for protocol method.
Krubsack 1989[265]	Unable to calculate values for 2x2 table (gives sensitivity and specificity values for locating adenomas in the correct region – 3 regions: right and left lobe of thyroid and below the thyroid gland)
Kucuk 2002[266]	Incorrect reference standard (presence of adenoma in people with positive imaging was only confirmed using histology – no mention of normocalcaemia to ensure no abnormal glands were missed)
Kukar 2014[267]	Unable to calculate 2x2 values for protocol method (accuracy in study based on laterality and not precise quadrant localisation). Incorrect reference standard (surgical cure was assessed but unclear if it was included as part of the reference standard)
Kuriloff 2004[269]	Unable to calculate sensitivity and specificity values.
Kutler 2011[270]	Incorrect reference standard (radiology reports and the operative and histopathologic findings).
Kuzu 2016[271]	Incorrect reference standard (histology)
Kwon 2013[272]	Incorrect reference standard (surgical findings and histology)
Lavely 2007[273]	Incorrect reference standard (surgical findings/determined by the surgeon)

Reference	Reason for exclusion
Lebastchi 2015[274]	Unable to calculate 2x2 table values for protocol method (number with correct localisation, localisation to wrong gland and negative on imaging given, but unclear if final outcome was single adenoma in all participants).
Lee 1996[277]	Incorrect population (16% had either secondary or tertiary HPT or MEN)
Lee 2016[275]	Unable to calculate 2x2 table values for protocol method.
Lenschow 2015[278]	Incorrect reference standard (intraoperative and pathologic finding. Incorrect index test (11C-Methionine PET/CT)
Leupe 2011[279]	Incorrect reference standard (surgical and pathological findings (also looked at pathology from one or more normal glands but unclear if all glands assessed in this way). Normocalcaemia following resection of a pathological gland was used to assume other glands normal, but suggested this was only done if unable to visualise all glands during the operation).
Levin 1987[280]	Incorrect population (27% had either MEN, secondary or tertiary HPT or familial HPT).
Lew 2009[281]	No accuracy data reported
Lew 2010[282]	Incorrect reference standard (no histological verification of adenomas, only IOPTH and post-operative normocalcaemia).
Lezaic 2014[283]	Unable to calculate 2x2 values for protocol method.
Lim 2017[284]	Gives sensitivity of IOPTH for predicting operative failure but not reported how operative failure was measured (unclear if normocalcaemia).
Lin 1991[285]	Incorrect population (people with hypercalcaemia and suspected parathyroid adenoma or carcinoma, and some included participants had chronic renal failure).
Linda 2012[286]	Incorrect reference standard (two reference standards used: surgical findings and histologic diagnosis).
Lindqvist 2009[287]	Unable to calculate sensitivity, specificity or 2x2 table values (methods state a ‘per-gland’ method and a ‘per-patient’ method, but results only given for the sensitivity and specificity of localising to the correct side).
Livingston 2014[288]	Not assessing accuracy of pre-operative imaging techniques
Lloyd 1990[289]	Incorrect reference standard (not all people had post-operative normocalcaemia).
Lubitz 2010[293]	Unable to calculate 2x2 values for protocol method.
Lumachi 2004[294]	Incorrect reference standard (IOPTH and final histology).
Lundstroem 2016[295]	Incorrect reference standard (quadrant of adenoma determined by anatomical findings at surgery, histopathological results and IOPTH). Normocalcaemia/hypercalcaemia at 1 year or more is reported but not included within the determination of the reference standard result.
Majors 1995[296]	Incorrect population (33% had secondary or tertiary HPT)
Malhotra 1996[297]	Incorrect population (29% had secondary or tertiary HPT)
Mandal 2015[298]	Unable to calculate 2x2 values for protocol method.
Mandell 2001[299]	Incorrect reference standard (accuracy of IOPTH for prediction of normocalcaemia, but no mention of pathological confirmation).
Manhire 1984[300]	Incorrect population (32% had MEN or family history of MEN).
Martin 1996[301]	Incorrect reference standard (compared with surgical and pathological findings, states the post-operative results were also reviewed but unclear if normocalcaemia/cure was assessed as part

Reference	Reason for exclusion
	of reference standard)
Martin 2000[302]	Incorrect reference standard (sustained post-operative normocalcaemia given as an outcome (% of people) but unclear if used as part of the reference standard to calculate accuracy of localisation).
Martinez-Rodriguez 2011[303]	Incorrect reference standard (histopathologic diagnosis).
Martinez-Rodriguez 2014[304]	Incorrect reference standard (histopathological result, unclear if normocalcaemia used as part of the reference standard)
Maweja 2004[305]	Incorrect reference standard (unclear reference standard as states all participants were normocalcaemic post-operatively, but also that there was 1 FP and 8TNs).
Mazzeo 2000[306]	Incorrect reference standard (histopathology).
McDermott 1996[307]	Incorrect population (6% had parathyroid carcinoma). Unable to calculate 2x2 table values for protocol method.
McDow, 2018 [308]	Review. Screened for relevant references.
McIntyre 1994[309]	Incorrect reference standard (unclear if histology and normocalcaemia used as part of the reference standard).
McMillan 1983[310]	Incorrect reference standard (normocalcaemia not mentioned).
Medas 2016[311]	Unable to calculate 2x2 values for protocol method.
Meyer 2009[312]	Comparison of 2 different IOPTH assays.
Mihai 2007[315]	Unable to calculate 2x2 values for protocol method (146/150 people had correctly localised adenoma but unclear if the imaging correctly located the adenoma in the other 4 people who were not cured after the first surgery).
Miller 2003[316]	Incorrect reference standard (normocalcaemia not reported in all people).
Mohammadi 2012[318]	Incorrect reference standard (post-operative histopathology results and IOPTH monitoring).
Moka 2000[319]	Unable to calculate 2x2 values for protocol method.
Moka 2000[320]	Unable to calculate 2x2 values for protocol method.
Morris 2012[322]	Incorrect reference standard (surgical results).
Mortenson 2008 [323]	Unable to calculate 2x2 values for protocol method.
Moure 2008 [324]	Unable to calculate 2x2 values for protocol method.
Mshelia 2012[326]	Not assessing the diagnostic accuracy of imaging to locate adenomas (correlation of imaging results with serum calcium levels)
Munk 2008[327]	Unable to calculate 2x2 table values for protocol method.
Murchison 1991[328]	Incorrect index test (US imaging using a 7.5MHz frequency probe).
Nael 2015[329]	Incorrect reference standard (surgical pathology).
Naik, 2018 [330]	Inappropriate reference standard (hypocalcaemia/hypercalcaemia is reported but unclear if normocalcaemia was assessed as part of reference standard).
Nair 2016[331]	Incorrect population (7% had carcinoma).
Najafian 2017[332]	Unable to calculate 2x2 values for protocol method.
Nasiri 2012[333]	Incorrect reference standard (histology only). Bilateral exploration performed and the decision to terminate the surgery was based on gross morphology in combination with frozen section – no use of cure/normocalcaemia to confirm absence of other abnormal glands
Nehs 2013[336]	Accuracy of IOPTH to correctly lateralise and not for precise localisation.

Reference	Reason for exclusion
Nelson 2007[337]	Incorrect study design. No relevant outcomes.
Neumann 1996[340]	Incorrect reference standard (surgical and histopathological findings).
Neumann 1997[339]	Incorrect reference standard (surgical and histopathological findings).
Neumann 1997[338]	Incorrect reference standard (surgical and histopathological findings).
Neumann 2008[341]	Incorrect reference standard (surgical findings and histology only).
Neves 2012[342]	Incorrect population (15.4% had MEN or carcinoma).
Niramitmahapanya 2018[344]	No relevant outcomes (study determines the cut-off values for IOPTH)
Noguchi 1994[345]	Paper not in English.
Noltes 2017[346]	For US and MIBI, can only deduce accuracy for lateralisation, not precise localisation. Incorrect index test (for IOPTH, a decrease of 65% was required)
Numerow 1995[348]	Incorrect population (primary or secondary HPT).
O'Connell 2011[349]	Unable to calculate values for 2x2 table (breakdown given of imaging results and surgical outcome, but imaging results only state left-sided or right-sided so unable to determine if imaging indicates 1 or more adenoma)
O'Doherty 1992[350]	No relevant outcomes (sensitivity, specificity or values for 2x2 table not provided).
Ohe 2003[351]	Incorrect index test (IOPTH results were not assessed while surgery was being performed). Average decline in PTH reported at each time point, and not number of people achieving >50% decline.
Opoku-Boateng 2013[352]	Unable to calculate sensitivity and specificity values.
Orevi 2014[353]	Incorrect population (only 50% of people had primary HPT).
Ozimek 2010[356]	Incorrect reference standard (gives diagnostic accuracy of IOPTH but unclear if normocalcaemia was used as the reference standard for all people, mentions subsequent cervical explorations and the accuracy for predicting 'operative outcome').
Ozkaya 2015[357]	Incorrect reference standard (normocalcaemia not part of reference standard; diagnosis confirmed by surgical resection, IOPTH, frozen section and histopathology)
Panzironi 2002[359]	Unable to calculate 2x2 table values for protocol method.
Parikh 2015[361]	Unable to calculate 2x2 table values for protocol method.
Parikh 2018[360]	Review. Screened for relevant references.
Pata 2010[362]	Unable to calculate 2x2 table for protocol method (study gives accuracy of SPECT and SPECT/CT for lateralisation and per-gland method).
Pata 2011[363]	Unable to calculate 2x2 table for protocol method (study gives accuracy of SPECT and SPECT/CT for lateralisation).
Patacsil 2006[364]	Unable to calculate 2x2 table values for protocol method.
Pattou 1998[366]	Incorrect index test (accuracy of venous sampling test in isolation, for lateralisation and not precise localisation).
Pattou 1999[367]	Incorrect index test (participants had either 99mTc-labelled sestamibi or 99mTc-labelled tetrofosmin). Unable to calculate sensitivity and specificity or 2x2 values for new method.
Pearl 1993[368]	Incorrect index test (methods of ultrasound not reported).
Peck 1987[369]	Unable to calculate 2x2 table for protocol method (study gives information on lateralisation of MRI).

Reference	Reason for exclusion
Pellitteri 2003[370]	Incorrect reference standard (surgical findings).
Perez-Monte 1996[371]	Incorrect reference standard (surgical and histopathologic findings)
Perrier 2000[372]	Incorrect population (secondary HPT, tertiary HPT, MEN and parathyroid cancer included). Incorrect index test (fine needle tissue aspirate).
Philippon 2014[373]	Incorrect population (MEN not excluded and unclear how many people had MEN)
Politz 2006[374]	Incorrect reference standard (pathology)
Powell 2013[375]	Incorrect reference standard (details of reference standard not reported). Unable To calculate 2x2 table for protocol method.
Prager 2003[376]	No accuracy results for IOPTH reported.
Prasannan 2007[377]	Unable to calculate 2x2 table for protocol method (accuracy of US and MIBI for correct lateralisation, not precise quadrant).
Preventza 2000[378]	Unable to calculate 2x2 table for protocol method (number classed as false negative by protocol method unclear).
Profanter 2004[380]	Incorrect index test (CAT-MIBI image fusion, unable to calculate 2x2 table values for protocol method for SPECT).
Profanter 2004[381]	Incorrect index test (CAT-MIBI image fusion, unable to calculate 2x2 table values for protocol method for SPECT).
Profanter 2004[379]	Incorrect index test ($^{99m}TcO_4$-$^{201}T1$ pinhole subtraction SPECT). Unable to calculate 2x2 table values for protocol method for US (unclear if a false positive in the study refers to an incorrect location or an additional normal gland localised).
Purcell 1999[382]	Unable to calculate 2x2 table values for protocol method (using 4-gland method).
Quiros 2004[383]	Incorrect reference standard (histopathology not reported).
Rameau 2016[384]	Incorrect reference standard (final pathology and IOPTH decline, not all patients were normocalcaemia after surgery)
Ramirez 2016[385]	Incorrect reference standard (pathology)
Raruenrom, 2018[386]	Incorrect reference standard-no normocalcaemia
Rauth 1996[387]	Incorrect reference standard (surgical and pathologic reports)
Reading 1982[388]	Not a human clinical study (study in dogs)
Reading 1985[389]	Incorrect population (15% had MEN, familiar disease or carcinoma).
Richards 2008[390]	Incorrect population (9% had MEN).
Rickes 2003[392]	Incorrect reference standard (surgery and histopathology).
Riss 2009[393]	Sensitivity, specificity and 2x2 table values not given for IOPTH.
Rodgers 2006[394]	Unable to calculate 2x2 table values for protocol method.
Rolighed 2004[395]	Incorrect index test (IOPTH drop of ≥80% at 5 minutes post-excision).
Roskies 2015[396]	Unable to calculate 2x2 table values for protocol method.
Rotstein 1998[398]	Incorrect population (7% of participants had carcinoma). Unable to calculate 2x2 values for protocol method.
Roza 1984[399]	Incorrect population (6% tertiary HPT). Incorrect reference standard (surgical and pathological findings – all normal looking glands biopsied but normocalcaemia not measured).
Rubello 2003[403]	No relevant outcomes (sensitivity, specificity or values for 2x2 table not provided).
Rubello 2005[402]	No relevant outcomes (sensitivity, specificity or values for 2x2 table not provided).

Reference	Reason for exclusion
Rubello 2006[400]	Unable to calculate 2x2 table values for protocol method.
Ruckert 1996[404]	Incorrect reference standard (unclear if normocalcaemia used as part of reference standard). Unable to calculate 2x2 values.
Ruf 2004[405]	Incorrect reference standard (histopathology only).
Ruf 2007[406]	Unable to calculate 2x2 table values for protocol method (unclear if scintigraphy results given in the table are the same for planar and SPECT).
Ryan 199 [407]	Unable to calculate 2x2 table values for protocol method.
Ryhanen 2015[408]	Unable to calculate 2x2 table values for protocol method (not all people cured, unable to confirm final diagnosis of single or multi-gland disease in all people).
Sadeghi 2008[410]	Unable to calculate 2x2 table values for IOPTH.
Sadeghi 2018[411]	Unable to calculate 2x2 table values for protocol method.
Sager 2014[413]	Incorrect reference standard (pathology only).
Saguan 2013[414]	Incorrect reference standard (histology only).
Saint Marc 2004[415]	Incorrect reference standard (not all people had normocalcaemia).
Sakimura 2013[416]	Incorrect reference standard (reference standard of cure based on post-operative PTH level, not serum calcium level).
Sand 1994[417]	Unable to calculate 2x2 table values for protocol method.
Sandqvist 2017[418]	Unable to calculate 2x2 table values for protocol method (paper uses a ‘per-gland’ method).
Sandrock 1990[419]	Incorrect reference standard (histopathology)
Schalin-Jantti 2013[420]	Incorrect reference standard (not all people had cure, therefore final pathology unclear). Unable to calculate 2x2 table values for protocol method.
Scheible 1981[421]	Incorrect population (people with hypercalcaemia suspected of having PHPT, but parathormone assays not routinely obtained).
Scheiner 2001[422]	Incorrect reference standard (histopathology and IOPTH)
Schenk 2013[423]	Unable to calculate 2x2 table values for protocol method.
Scott-Coombes 2017[424]	Sensitivity and specificity of IOPTH reported separately for people with negative and positive pre-operative imaging (overall sensitivity and specificity or 2x2 table values not reported).
Sebag 2003[425]	Unable to calculate 2x2 table values for protocol method (unclear numbers used to calculate sensitivity for IOPTH, so unable to determine 2x2 table values).
Seeliger 2015[426]	Unable to calculate 2x2 table values for protocol method.
Seniaray 2016[427]	Incorrect study design (case report). Incorrect index test (PET scan)
Sepahdari 2015[428]	Unable to calculate 2x2 table values for protocol method.
Serra 2006[429]	Paper not in English
Seyednejad 2016[430]	Unable to calculate 2x2 table values for protocol method.
Shabtai 2003[431]	Unable to calculate 2x2 table values for protocol method.
Shafiei 2012[432]	Incorrect population (6% had MEN). Unable to calculate 2x2 table values for protocol method (per-gland method used).
Shaha 1997[433]	Unable to calculate 2x2 table values for protocol method.
Shaheen 2008[434]	Unable to calculate 2x2 table values for protocol method.
Sharma 2006[435]	Unable to calculate sensitivity, specificity or 2x2 values for protocol method.
Sharma 2008[436]	Incorrect reference standard (a proportion of people had unclear

Reference	Reason for exclusion
	pathology, therefore unable to assess the accuracy of IOPTH).
Sheng 2011[437]	Paper not in English
Shin 2011[438]	Incorrect population (included people with secondary and tertiary hyperparathyroidism, MEN and parathyroid cancer).
Sho 2016[439]	Unable to calculate 2x2 table values for protocol method.
Silov 2013[440]	Incorrect reference standard (histology only). No relevant outcomes. Not looking at accuracy for correctly localising the adenoma, but for correctly predicting the presence of an adenoma (at any location).
Singh 2007[441]	Incorrect reference standard (histopathology)
Siperstein 2004[443]	Unable to calculate 2x2 table values for protocol method.
Siperstein 2008[442]	Unable to calculate 2x2 table values for protocol method.
Slater 2005[444]	Unable to calculate 2x2 table values for protocol method.
Smith 2009[445]	Incorrect reference standard (normocalcaemia not reported)
Sofferman 1996[446]	Incorrect reference standard (surgical and pathological findings)
Sofferman 1998[447]	Accuracy measures or 2x2 table values for IOPTH not reported.
Sofianides 1978[448]	Incorrect index test (cervical oesophagram). Incorrect reference standard (histology only).
Sohn 2015[449]	Assessing the difference between IOPTH decline in people with PHPT and renal insufficiency and people with PHPT without renal insufficiency (although the 2x2 table can be calculated for the group without renal insufficiency, the study only included people with single adenoma who were cured – no reference standard negative).
Sokoll 2000[450]	Incorrect reference standard (for IOPTH, no mention of pathology, unclear if histology used to confirm final outcome).
Solorzano 2005[452]	Incorrect reference standard (IOPTH, macroscopic evaluation and post-operative normocalcaemia but without histopathology).
Solorzano 2006[451]	Incorrect reference standard (post-operative normocalcaemia but without histopathology).
Sommer 1982[453]	Unable to calculate 2x2 values for protocol method.
Song 1999[454]	Incorrect reference standard (surgical and pathologic findings).
Soon 2008[455]	Unable to calculate 2x2 table values for protocol method (study looked at accuracy for localisation of the correct side, not precise quadrant).
Soyder 2015[456]	Unable to calculate 2x2 table values for protocol method.
Sreevathsa 2017[458]	Incorrect population (secondary and tertiary hyperparathyroidism included).
Starker 2011[460]	Incorrect population (15% had familial hyperparathyroidism). Unable to calculate 2x2 table values for protocol method.
Starr 2001[461]	Incorrect population (included people with secondary HPT, MEN and carcinoma).
Staudenherz 1997[462]	Incorrect reference standard (histopathology – 'a biopsy of a normal gland was also taken for reference' but normocalcaemia not measured).
Stein 1990[463]	Incorrect population (people with secondary and tertiary HPT included). Incorrect reference standard (operative and histologic findings).
Stevens 1993[465]	Incorrect reference standard (surgical and pathological findings).
Steward 2006[466]	Unable to calculate 2x2 table values for protocol method.
Stratmann 2002[467]	Incorrect reference standard (accuracy of IOPTH in relation to post-

Reference	Reason for exclusion
	operative serum calcium, but no mention of histology).
Suarez 2017[468]	Unable to access full text paper
Sugg 1993[469]	Incorrect reference standard (unclear if normocalcaemia used as part of the reference standard for all people, to confirm all adenomas removed).
Sugg 2004[470]	Unable to calculate 2x2 table values for protocol method (accuracy for lateralisation not precise localisation).
Suh 2015[471]	Unable to calculate 2x2 table values for protocol method.
Sullivan 2001[472]	Incorrect population (6% had secondary HPT or papillary thyroid carcinoma). Unable to calculate 2x2 table values for protocol method.
Sun 2016[473]	Incorrect population (people with MEN included in study population but unclear if included in the people with surgery who underwent final analysis). Incorrect reference standard (not all people rendered normocalcaemic by surgery and further investigation not reported).
Taira 2004[474]	Incorrect reference standard (histopathology).
Takei 1999[475]	Incorrect reference standard (normocalcaemia not reported). Incorrect population (1 participant out of 15 had MEN).
Taylor 1996[477]	Incorrect index test (accuracy of venous sampling test in isolation, for lateralisation and not precise localisation).
Taywade 2017[478]	Incorrect reference standard (histopathology).
Tee 2013[479]	Unable to calculate 2x2 table values for protocol method.
Thakur 2009[480]	Incorrect reference standard (accuracy of IOPTH reported but unclear reference standard, details not reported).
Thanseer 2017[481]	Incorrect reference standard (no confirmation that all people were normocalcaemic post-operatively).
Thielmann 2017[482]	No accuracy data reported for IOPTH.
Thomas 2009[483]	Incorrect reference standard (histology).
Thompson 1999[484]	Incorrect population (19% had MEN or familial disease).
Thule 1994[485]	Incorrect population (included people with primary or secondary HPT).
Tokmak 2014[487]	Incorrect reference standard (surgical findings).
Toriie 2016[488]	Incorrect reference standard (unclear if all had normocalcaemia).
Treglia 2016[489]	Incorrect reference standard (systematic review – normocalcaemia as part of the reference standard was not an inclusion criteria for studies)
Treglia 2018[490]	Review article – unable to obtain full text
Trinh 2017[491]	Incorrect reference standard -data given for recurrence on follow-up (hypercalcaemia at ≥6 months), not for operative cure
Tublin 2009[492]	Incorrect reference standard (surgery and pathology reports, surgical failure based on IOPTH, no details of post-operative normocalcaemia)
Tummers 2015[493]	Incorrect reference standard (presence of adenomas were confirmed using histology of resected specimen and IOPTH, but no use of normocalcaemia/cure, so unable to eliminate the possibility of further adenomas)
Tunca 2017[494]	Unable to calculate 2x2 table values for protocol method.
Tziakouri 1996[495]	Incorrect reference standard (histopathology)
Udelsman 2003[496]	Incorrect reference standard (no details of reference standard given for positive confirmation of abnormal gland)

Reference	Reason for exclusion
Ulanovski 2002[497]	Incorrect reference standard (pathology)
Untch 2011[498]	Unable to calculate 2x2 table values for protocol method (accuracy of US and MIBI for lateralisation not precise localisation).
Valdemarsson 1998[499]	Unable to calculate 2x2 table values for protocol method (accuracy of scintigraphy for lateralisation not precise localisation).
Van Dalen 2001[500]	Unable to calculate 2x2 table values for protocol method.
Van der Vorst 2014[501]	Incorrect reference standard (histopathology)
Vaz 2011[503]	Incorrect reference standard (unclear what was used for the reference standard)
Vitetta 2014[505]	Unable to calculate 2x2 table values for protocol method.
Von Schulthess 1988[506]	Incorrect reference standard (surgical and pathological findings).
Wachtel 2015[507]	Incorrect index test (for IOPTH, accuracy only reported for a drop of 50% and into the normal range – unable to calculate for a 50% drop alone)
Weber 1993[510]	Incorrect population (29% had either secondary hyperparathyroidism or MEN)
Weber 1999[509]	Incorrect index test (IOPTH samples taken but results not available until 48 hours (not available intraoperatively for decision making).
Weber 2004[511]	Incorrect population (around 50% had secondary HPT).
Weber 2010[512]	Incorrect reference standard (intraoperative and histological findings). Unable to calculate sensitivity and specificity for protocol method.
Weber 2013[514]	Incorrect index test (C-11 Methionine PET/CT). Unable to calculate 2x2 table values for protocol method for US.
Weber 2017[513]	Incorrect index test (assessing the accuracy of Methionine PET/CT, unable to calculate 2x2 table values for US and only selected patients with a negative MIBI)
Wei 1992[516]	Incorrect reference standard (histopathology). Incorrect population (20% had secondary or tertiary HPT and were analysed with the results of people with multigland primary HPT).
Wei 1994[517]	Incorrect population (43% had either MEN, secondary hyperparathyroidism or tertiary hyperparathyroidism and results mixed)
Wei 2015[518]	Incorrect reference standard (systematic review – normocalcaemia as part of the reference standard not required as an inclusion criteria of the studies).
Westerdahl 2004[519]	Unable to calculate 2x2 table values for protocol method.
Westra 1998[520]	Incorrect reference standard (histopathology)
Wheeler 1982[521]	Unable to calculate 2x2 table values for protocol method.
Whelan 1989[522]	Incorrect population (25% of people had MEN). Accuracy for lateralisation of MRI and US, not precise localisation.
Whitley 1981[523]	Can calculate the accuracy for predicting the correct side of adenoma location, but not the precise quadrant.
Witteveen 2010[525]	Incorrect population (50% had tertiary HPT, MEN or parathyroid carcinoma).
Wong 2009[527]	Unable to calculate 2x2 table values for protocol method.
Wong 2011[528]	Diagnostic accuracy of US and MIBI for correct lateralisation of the adenoma, not for localisation of the abnormal gland
Wong 2015[526]	Incorrect reference standard (systematic review – normocalcaemia as part of the reference standard was not an inclusion criteria for studies)

Reference	Reason for exclusion
Woods 2017[529]	Incorrect reference standard-no normocalcaemia
Wu 1988[530]	Incorrect reference standard (unclear if normocalcaemia used as part of the reference standard)
Yan 2018[531]	Incorrect reference standard (unclear if normocalcaemia used as part of the reference standard)
Yao 1993[532]	Unable to calculate 2x2 table values for protocol method.
Yen 2006[534]	Incorrect reference standard (reference standard for IOPTH for 'failed operations' included people who were initially normocalcaemia but were then hypercalcaemic after 6 months (recurrent PHPT).
Yen 2008[533]	Incorrect population (13% had MEN or parathyromatosis).
Yip 2008[535]	Unable to calculate 2x2 table values for protocol method.
Younes 2008[536]	Incorrect reference (intraoperative and histopathology).
Zawawi 2013[538]	Incorrect reference standard (pathology and drop in IOPTH but no use of cure/normocalcaemia) Presence of adenoma confirmed if frozen section showed hyper cellular gland or adenoma and the IOPTH dropped. If IOPTH did not drop then other glands were explored.
Zeina 2017[539]	Unable to calculate 2x2 table values for protocol method.
Zerizer 2011[540]	Incorrect reference standard (histopathology).
Zhang 2018[541]	Systematic review- screened for relevant references
Zmora 1995[542]	Incorrect index test (US with a 7MHz scanner and scintigraphy with radio iodinated toluidine blue-technetium 99m or thallium 201-technetium 99m).
Zotti 1984[543]	Incorrect reference standard (no details reported).

J.2 Excluded health economic studies

None.