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GUIDELINES

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Primary hyperparathyroidism in adults—(Part I) assessment and medical management: Position statement of the endocrine society of Australia, the Australian & New Zealand endocrine surgeons, and the Australian & New Zealand bone and mineral society

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Abstract

Objective: To formulate clinical consensus recommendations on the presentation, assessment, and management of primary hyperparathyroidism (PHPT) in adults.

Methods: Representatives from relevant Australian and New Zealand Societies used a systematic approach for adaptation of guidelines (ADAPTE) to derive an evidence-informed position statement addressing nine key questions.

Results: PHPT is a biochemical diagnosis. Serum calcium should be measured in patients with suggestive symptoms, reduced bone mineral density or minimal trauma fractures, and in those with renal stones. Other indications are detailed in the manuscript. In patients with hypercalcaemia, intact parathyroid hormone, 25-hydroxy vitamin D, phosphate, and renal function should be measured. In established PHPT, assessment of bone mineral density, vertebral fractures, urinary tract calculi/nephrocalcinosis and quantification of urinary calcium excretion is warranted. Parathyroidectomy is the only definitive treatment and is warranted for all symptomatic patients and should be considered for asymptomatic patients without contraindications to surgery and with >10 years life expectancy. In patients who do not undergo surgery, we recommend annual evaluation for disease progression. Where the diagnosis is not clear or the risk-benefit ratio is not obvious, multidisciplinary discussion and formulation of a consensus management plan is appropriate. Genetic testing for familial hyperparathyroidism is recommended in selected patients.

Conclusions: These clinical consensus recommendations were developed to provide clinicians with contemporary guidance on the assessment and management of PHPT in adults. It is anticipated that improved health outcomes for individuals and the population will be achieved at a decreased cost to the community.

KEYWORDS
asymptomatic hyperparathyroidism, bone density, hypercalcemia, hyperparathyroidism, parathyroid carcinoma, parathyroidectomy, parathyroid hormone, renal calculi

1 | INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common disorder with a significant health burden that arises from autonomous overproduction of parathyroid hormone (PTH) by abnormal parathyroid glands. It is characterised by the elevation of serum calcium levels with elevated or inappropriately normal PTH levels. There have been substantial changes in clinical presentation, understanding of the natural history and medical and surgical management over recent decades, with most recent international guidelines published

between 2014 and 2016.[1–6] The aims of this position statement are to give updated guidance in contentious emerging areas of practice and to adapt existing guidelines to better reflect the practice environment of Australia and New Zealand.

The position statement is divided into two parts: Part I Assessment and Medical Management and Part II Surgical Management and Postoperative Follow-Up. Representatives from the Endocrine Society of Australia (ESA), the Australian & New Zealand Endocrine Surgeons (ANZES) and the Australian & New Zealand Bone and Mineral Society (ANZBMS) were tasked to review and adapt guidelines using a systematic approach proposed by the ADAPTE working group[7] to formulate clinical consensus recommendations on presentation, assessment, and both medical and surgical management of primary hyperparathyroidism in adults. It is expected that better health outcomes for individuals and the population will be achieved in a more standardised manner and at a decreased cost to the community.

2 | PURPOSE AND SCOPE

This position statement is primarily intended for use by general practitioners, endocrinologists and endocrine surgeons. Medical practitioners in other specialties, such as general physicians, nephrologists, urologists and geriatricians, will also come across patients with PHPT, and may find these guidelines useful.

Part I of II of this position statement focuses on the presentation, assessment, and nonsurgical management of PHPT in adults, including specific considerations such as pregnancy and familial hyperparathyroidism. Specifically, we address the following key questions:

1. *Who Should Be Evaluated for Primary Hyperparathyroidism?*
2. *What are the Diagnostic Investigations and Criteria?*
3. *What are the Ancillary Target Organ Investigations?*
4. *Who Should Be Referred for Surgery?*
5. *What is the Management of Asymptomatic Hyperparathyroidism?*
6. *How Does the Management of Hyperparathyroidism in Pregnancy Differ?*
7. *When Should Parathyroid Carcinoma Be Suspected?*
8. *When Should Familial Hyperparathyroidism Be Suspected and What is the Role for Genetic Testing?*

Part II of this position statement (published separately) focuses on the surgical, peri-operative and long-term management of PHPT in adults.

3 | METHODS

The Councils of ESA, ANZES and ANZBMS invited expert representatives of the respective societies and additional authors with expertise in this field (radiology, nuclear medicine and pathology) to participate in a working group in 2020. An experienced academic endocrinologist (MG) was selected to chair the working group. A consumer representative was invited to participate and highlight priorities, and to write a perspective (see Supporting Information Appendix S1).

One face-to-face meeting, before COVID-19 state restrictions, was held in March 2020. Subsequent communication within the working group was accomplished by email and virtual meetings, due to the COVID-19 pandemic. All potential conflicts of interests of participating authors were declared before commencing drafting of the manuscript (Table S1).

Two authors (JG and SH) performed the initial search and review of previous guidelines with support from the Wellington Health and Medical Sciences Library (University of Otago). A systematic search of medical databases (Medline, Embase, Scopus and Cochrane Database of Systematic Reviews) was performed from 2010 to 2019, published in the English language and using an exhaustive list of search terms (see Supporting Information Appendix S2 for an example of an unedited Medline search). When combining database results, 2155 references were initially identified which was reduced to 370 upon manual review of relevance and then 142 after removal of duplicates. Further manual review by two authors (JG and SH) limited to guidelines and/or consensus statements identified 21 publications deemed appropriate for inclusion.

The 21 identified guidelines were independently ranked in order of relevance by each member of the Steering Group (MG, FM and JM) and the 12 highest ranked guidelines were reviewed by a further group of delegates (JG, SH, SF, CG, SDS, JS, FM and MG) and rated according to the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument and overall assessment (Table S2). The scores for each domain were averaged based on the number of responses for each domain and guideline. Based on this assessment, the Steering Group devised a list of questions to be answered. All members responded and discussed these questions at a face-to-face session held in March 2020, and questions were allocated to subgroups of members. While ADAPTE methodology was used as the basis to inform our recommendations, given the large number of local experts involved in generating our recommendations, and the independent feedback from the councils of the three stakeholder societies, the final recommendations are shaped by consensus opinions reflecting the collective expertise inputed into the final manuscript. We cannot report levels of evidence and Grading of Recommendations, Assessment, Development and Evaluation as we did not perform the original data extraction. Therefore, we do not provide evidence levels and refer readers to the original documents as needed.

All authors contributed to the writing of the manuscript and the final draft statement was agreed to by all authors. While the stakeholder was given the opportunity to review and comment on the manuscript, the stakeholder declined coauthorship to preserve their anonymity. External review was sought, and the draft statement was then submitted to the Councils of ESA, ANZES and ANZBMS who provided feedback. The working group responded to feedback and

the final version was endorsed in August 2021. This position statement will be reviewed and updated in 10 years or sooner if significant changes occur.

4 | THE POSITION STATEMENT

4.1 | Section A: Diagnosis and evaluation

Primary hyperparathyroidism may be suspected and diagnosed because of symptoms, the presence of osteoporosis or kidney stones or it may be an incidental biochemical finding. Reference to mild or severe PHPT is sometimes used, without standard definition.

Bilezikian et al.[8] have described three clinical phenotypes (which combine different aspects of classification): (1) overt target organ involvement (usually associated with classical PHPT); (2) mild asymptomatic hypercalcaemia and (3) normocalcaemic PHPT.

We classify PHPT according to the following two variants:

1. Classical PHPT: is defined by elevated serum calcium with elevated serum PTH, associated with parathyroid neoplasia—either single or multiple adenomas, or multiglandular hyperplasia. End-organ effects depend upon duration and severity of the disease. Surgical removal of neoplastic parathyroid tissue will correct hypercalcaemia and its symptoms and improve end-organ damage.[8] Elevated serum calcium associated with inappropriately normal serum PTH (sometimes referred to as normohormonal hyperparathyroidism, NHHPT) is usually included within classical PHPT, and may represent up to 25% of all PHPT.[9,10] Multiglandular disease may be more common in NHHPT.[10] It is important to differentiate FHH from this condition by measuring urinary calcium excretion.

2. Normocalcaemic HPT (NCHPT): is defined by elevated serum PTH and serum adjusted and ionised calcium consistently within the normal reference range, normal renal function, and the absence of other secondary causes of hyperparathyroidism (including vitamin D insufficiency/deficiency, renal impairment, idiopathic hypercalciuria, malabsorption, Paget's disease and iatrogenic causes—thiazides, lithium, denosumab and bisphosphonates).[2] Although data on natural history of NCHPT are sparse and inconsistent, some patients with NCHPT will develop classical HPT over time. NCHPT is relatively common in postmenopausal women (between 0.1% and 8.9%)[11,12] and often associated with low BMD at lumbar spine, femoral neck and distal radius (in contrast to classical HPT which is associated with preferential bone loss at cortical sites).[13] When associated with definite parathyroid neoplasia, surgery for NCHPT will correct hyperparathyroidism and modestly increase BMD.[14]

Symptoms and end-organ complications are more likely with classic PHPT and higher calcium levels but there is not a strong correlation. All patients should be assessed in the same manner.

Each of these variants may be symptomatic or asymptomatic and may be associated with single or multiple adenomas, or multiglandular hyperplasia. Any of these clinical variants may be associated with hereditary causes of hyperparathyroidism (see Chapter 8).

4.1.1 | Who should be evaluated for primary hyperparathyroidism?

The prevalence of primary hyperparathyroidism can be between 17 and 94.6 per 100,000 patient-years, with differences in age, sex and ethnicity contributing to the observed variability;[15] older age, female sex, Asian and Black ethnicities are risk factors.[16] In elderly populations, the prevalence of hyperparathyroidism may be up to 1.5%.[17] In developed nations, the classical presentation of primary hyperparathyroidism with renal stones, abdominal symptoms and bone complications is seen less frequently since introduction of automated calcium measurements in the 1970s.[16] Currently, most patients with PHPT have mild, nonspecific symptoms, or may be asymptomatic. However, nonspecific sympoms (such as fatigue) may co-exist with rather than being causally related to PHPT, especially if mild. While calcium is not part of most routine panels for electrolytes and renal function in many countries, including Australia, there are several patient groups where measurement of serum calcium is indicated. While some estimates suggest that the prevalence of classical primary hyperparathyroidism is around 1%,[15,16] prevalence data from Australia and New Zealand are not available. Whether population screening with serum calcium is justified in patients >50 years old is an area for further study. Of note, there is a broad population of patients in whom serum calcium should be measured, as summarised below.

Recommendation 1.1: Serum calcium should be measured in patients with reduced bone mineral density.

All patients with osteoporosis, and young patients with low bone mass (defined by dual-energy X-ray absorptiometry (DXA) derived bone mineral density (BMD) Z-score of less than −2.0) should be screened for PHPT. DXA measurement should include the forearm, as PHPT can be associated with disproportionate bone loss at this site.[18] Operative cure of primary hyperparathyroidism leads to a sustained improvement of BMD[19–22] and reduced fracture risk.[23–26]

Recommendation 1.2: Serum calcium should be measured in patients who present with minimal trauma fractures.

Patients presenting with minimal trauma fractures (defined as fractures resulting from a fall from a standing height or less, excluding those of digits the skull and including morphometric vertebral fractures) are frequently under-investigated and under-treated.[27] Hypercalcaemia will be present in some of these patients and contribute to increased bone fragility, even in the absence of osteoporosis by DXA criteria.[28]

Recommendation 1.3: Serum calcium should be measured in patients with renal stones.

Hypercalcaemia with consequent hypercalciuria will increase the probability of calcium oxalate renal stones. Rejnmark et al.[29] reported that nephrolithiasis was present in approximately 7% of patients with otherwise asymptomatic PHPT as compared to 1.6% among patients without PHPT.[29] Other studies using US scanning show renal stones in up to 55%.[30]

Recommendation 1.4: Serum calcium should be measured in patients taking lithium.

Lithium usage is strongly associated with an increased incidence of PHPT. There is insufficient population-based data to determine

the true prevalence of PHPT in patients treated with lithium and estimates vary widely. In a retrospective study, the prevalence of hypercalcemia in patients with bipolar disorder treated with lithium was 26.2% (82/313) compared to 1.4% (2/137) in patients with bipolar disorder not treated with lithium.[31] In patients on chronic lithium therapy calcium levels should be monitored annually.

Recommendation 1.5: Serum calcium should be measured in patients with fatigue, musculoskeletal or neuropsychiatric complaints or altered mental status.

PHPT should be considered in the differential diagnosis of patients who present with nonspecific symptoms such as fatigue, gastrointestinal symptoms such as nausea, constipation, and vague abdominal pain, musculoskeletal symptoms including muscle, bone and joint pains and weakness, and neuropsychiatric complaints[32] such as depression, anxiety, mood swings, difficulty with memory and concentration and irritability especially if they are >40 years of age. Although most of these patients will not have PHPT, the ones who do can be treated appropriately only if the diagnosis is made. However, whether such nonspecific symptoms are caused by PHPT, or due to other coexisting comorbidities (e.g., depression) is often difficult to determine, especially if serum calcium is only modestly elevated. In prospective studies, either uncontrolled or compared to thyroidectomy parathyroidectomy has been reported to improve musculoskeletal[33] and neuropsychiatric[34] symptoms of PHPT, but high level RCT evidence is lacking. Measurement of serum calcium concentrations is also recommended in those presenting with psychiatric illness or dementia.[35,36]

Recommendation 1.6: Serum calcium, PTH, and 25-hydroxy vitamin D should be measured in patients >40 years before undergoing thyroid surgery.

Thyroid and parathyroid disease are both common, with a similar peak demographic. While high level evidence to support this approach is lacking, it may be prudent to screen for PHPT in patients before thyroidectomy as well as checking for secondary HPT, most commonly from vitamin D deficiency. It is not uncommon for a surgeon to come across an incidentally enlarged or borderline enlarged parathyroid gland during thyroidectomy,[37] and knowledge of the patient's calcium and PTH status is necessary for an informed decision whether to spare or resect the parathyroid gland in question. In addition, there is an increased surgical risk associated with revision surgery, which may occur when a patient is diagnosed with primary hyperparathyroidism after previous thyroidectomy.

Recommendation 1.7: Serum calcium should be checked in patients with malignancy.

A number of malignancies are associated with hypercalcaemia, most commonly breast, renal, or lung cancer, melanoma and multiple myeloma. Production of parathyroid hormone related protein and lytic bone metastases may occur, particularly in patients with advanced disease. Concomitant PHPT may also occur in patients with malignancy,[38] with a reported frequency of PHPT in up to 7% in women with treated breast cancer. The measurement of PTH together with calcium will identify the subgroup that have primary hyperparathyroidism. Diagnosis of PHPT is particularly important in postmenopausal women with receptor positive breast cancer treated with aromatase inhibitors, which also accelerate bone loss. There is some evidence that the incidence of PHPT in these patients is higher than expected.[39]

4.1.2 | What are the diagnostic investigations and criteria?

Mildly symptomatic, or even asymptomatic disease is now the predominant clinical presentation,[40,41] therefore appropriate laboratory investigations establish the diagnosis. Measurement of hypercalcaemia with elevated or inappropriately normal parathyroid hormone level makes PHPT the most likely diagnosis.

Recommendation 2.1: Measure albumin-adjusted serum calcium in patients with normal renal function and albumin levels; otherwise add ionised calcium.

Measurement of albumin-adjusted serum calcium is recommended, as ~40% of calcium is bound to albumin, and total calcium concentrations change in parallel to serum albumin concentrations. However, adjustment for albumin can lead to overcorrection and falsely diagnosed hypercalcemia,[42,43] in those with poor renal function and where albumin levels are less than 30 g/L. The gold standard for measuring calcium in the blood is ionised calcium corrected for pH. It is the ionised fraction of calcium that feeds back to the calcium sensing receptor and decreases secretion of PTH. The fact that measurement of ionised calcium is currently not automated, along with a requirement for anaerobic collection and processing within 2 h of collection, have led to underutilisation of this test. Up to 10% of patients with PHPT have normal serum calcium but elevated ionised calcium levels and PTH.[44] If the corrected serum calcium is normal and PTH is elevated, serum ionised calcium should be measured, unless there is a potential alternative explanation for an elevated PTH (e.g., untreated vitamin deficiency, renal impairment, denosumab use).

Recommendation 2.2: In patients with elevated albumin-adjusted calcium, repeat the test (or request ionised calcium) with serum phosphate, renal function, PTH and 25-hydroxy vitamin D levels.

The albumin-adjusted serum calcium measurement should be repeated at least once if the first measurement is close to the upper limit of the local reference range, equating to 2.6 mmol/L in most Australian laboratories. Ionised calcium can be used to confirm hypercalcaemia. Typically, in PHPT serum phosphate levels checked at the time of calcium testing are low. Electrolytes, renal function, and 25-hydroxy vitamin D levels should be measured at the same time.

Intact PTH assays measure PTH using 2 antibodies against a more N-terminal and a mid-regional epitope of PTH. More recently so-called whole PTH assays have become available. These assays utilise an antibody against the first three amino acids in combination with a mid-regional PTH antibody.[45] There is no assay interference by PTH fragments that circulate in renal failure. There is no evidence that these assays identify PHPT better than intact PTH assays. PTH should always be concurrently measured with calcium or ionised calcium levels.

Recommendation 2.3: In patients with confirmed hypercalcemia, measure urinary calcium:creatinine clearance ratio on 24-h urinary calcium or a second morning void urinary calcium:creatinine ratio to differentiate hyperparathyroidism from familial hypercalcemic hypocalciuria (FHH).

Excluding hypocalciuria is important to distinguish PHPT from familial FHH.[46] FHH should be considered in patients with long-standing hypercalcemia with either (1) spot or 24 h urine calcium:-creatinine clearance ratio (CCCR) < 0.01 or (2) 24 h urinary calcium levels <100 mg/24 h (2.5 mmol/24 h)[47,48] CCCR is considered the biochemical test of choice and a CCCR < 0.01 is specific for FHH, but it is not sensitive. Most patients with PHPT have a CCCR > 0.02, however, a considerable overlap exists and a combination of clinical suspicion, calcium excretion and genetic testing might be required for correct diagnosis in difficult cases. Patients should have normalised 25-hydroxy vitamin D and have discontinued medications that interfere with calcium excretion such as thiazides.

4.1.3 | What are the ancillary target organ investigations?

Classical descriptions of bone disease in PHPT included osteitis fibrosis cystica, with symptoms of bone pain, skeletal deformities, and pathological fractures. Overt clinical presentations of bone disease are now less common, especially in developed countries. However, epidemiological studies of patients with PHPT demonstrate increased fracture risk at all skeletal sites.[49,50] Reductions in BMD using DXA are seen, particularly at cortical skeletal sites such as the distal radius.[51] Newer technologies such as DXA-derived trabecular bone score (TBS) and high-resolution peripheral quantitative computed tomography (HR-pQCT) have documented more extensive skeletal involvement even in patients without overt skeletal manifestations.[52] Therefore, assessment of skeletal health remains an important consideration in PHPT.

Recommendation 3.1a: For individuals with a diagnosis of primary hyperparathyroidism, a DXA scan of the hip, lumbar spine, and distal radius is recommended.

While also common in the general population of older individuals, reduced BMD on DXA is a well-established end organ complication of PHPT and is therefore recommended for routine screening of individuals with PHPT. Specific assessment of the distal radius is important, as it is often the most affected site.[49,53] Though TBS and HR-pQCT provide additional insights into bone microarchitecture in PHPT, further research is required before these modalities are recommended in the routine evaluation of bone disease in PHPT.

Recommendation 3.1b: All PHPT patients should receive a thoracolumbar imaging at baseline. Parathyroidectomy should be considered in patients with vertebral compression fracture (either symptomatic or asymptomatic).[19]

A significant proportion of vertebral compression fractures are asymptomatic. The presence of vertebral fractures in the absence of a prior history of back trauma indicates a significant degree of skeletal fragility independent of DXA derived BMD and has management implications for PHPT. More than a third of patients with PHPT may demonstrate evidence of vertebral fractures on initial evaluation.[30,54]

Recommendation 3.2a: Renal tract imaging should be considered for patients with PHPT without other indications for parathyroidectomy. Available modalities include renal tract ultrasound and X-ray KUB. Non-contrast CT scan (CT-KUB), has relatively little radiation exposure and excellent sensitivity.

Nephrolithiasis may be asymptomatic in patients with PHPT and has treatment implications, with a potential decline in kidney function over time. There is variability in the reported prevalence of nephrolithiasis (7%–55%),[29,30] depending on the patient cohort and utilised imaging modality. A study of 184 patients with urolithiasis who underwent evaluation with both ultrasound and low-dose CT demonstrated that CT had higher sensitivity (97.2%) compared with ultrasound (75.5%).[55] The presence or absence of urinary tract calculi or nephrocalcinosis can then inform therapeutic decision-making.

Recommendation 3.2b: Even in the absence of a history of urinary tract calculi or detection on imaging, urinary calcium excretion may be assessed. Parathyroidectomy may be considered in patients with confirmed hyperparathyroidism and hypercalciuria.

Urinary tract calculi are possibly more likely to precipitate when urine calcium is higher.[56] Although renal insufficiency and nephrocalcinosis do not resolve following parathyroidectomy, surgery may prevent a further decline in the glomerular filtration rate. The urine calcium excretion is associated with increased risk of renal stones above 5 mmol/24 h and risk increases dependent on the degree of hypercalciuria.[57] The 4th workshop on management of pHPT suggested a cutpoint of 24 h urine calcium level >10 mmol/day (>400 mg/day).

4.1.4 | Who should be referred for surgery?

Surgery is the only definitive treatment of PHPT. Parathyroidectomy is indicated for all symptomatic patients who are fit for surgery, in those with osteoporosis on DXA criteria or fragility fracture, in those with nephrolithiasis, nephrocalcinosis and those with deteriorating renal function, and suggested for those with a glomerular filtration rate (GFR) of <60 ml/min, in the absence of another explanation. An algorithm of a suggested approach to the patient with PHPT is available in Figure 1.

Parathyroidectomy is indicated for all asymptomatic patients <50 years old, and should be considered for asymptomatic patients who are fit for surgery and have a life expectancy of ten years or more. Patients initially thought to be asymptomatic may experience improved quality of life after parathyroidectomy.[58–60]

The diagnosis of PHPT is biochemical, and not reliant upon corroborative imaging. Patients who meet criteria for surgery should be referred for a specialist surgical opinion regardless of imaging results. Often, specialist parathyroid surgeons prefer to organise imaging

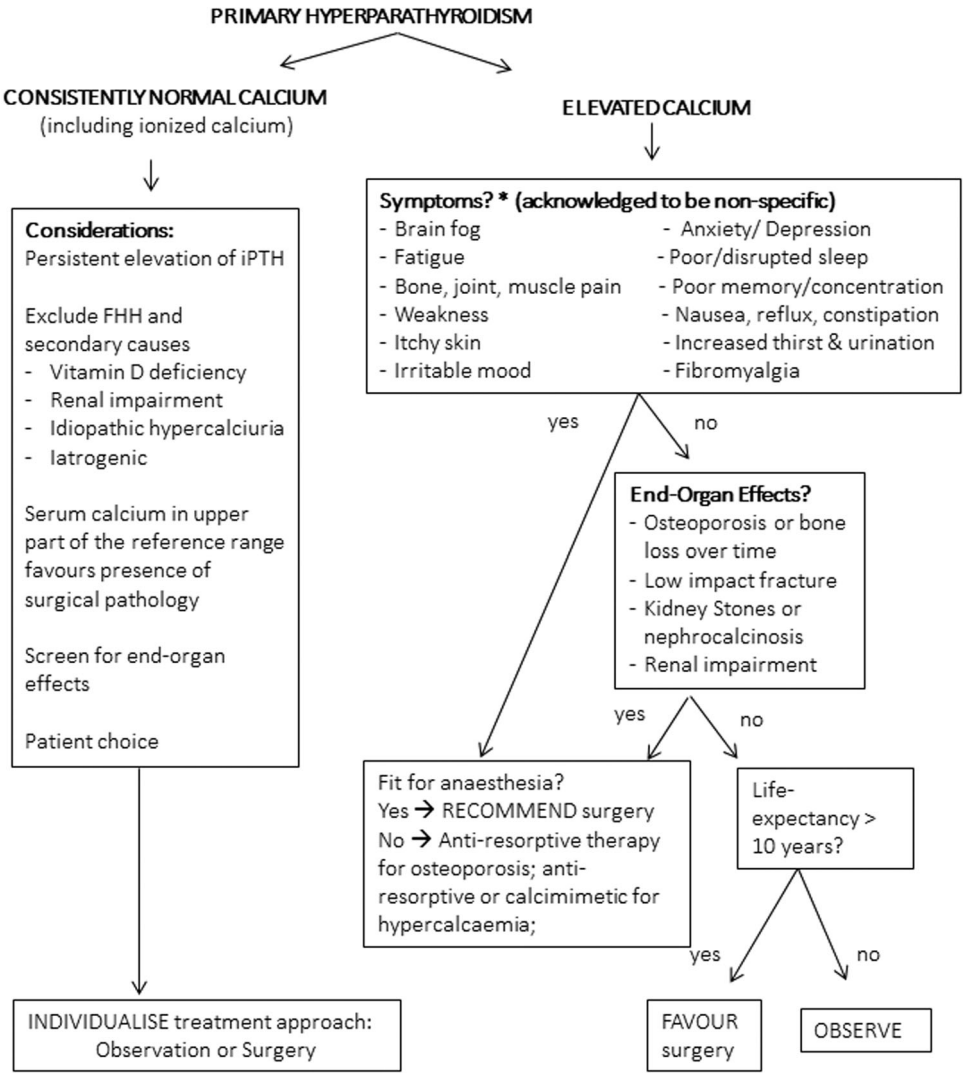

FIGURE 1 Management algorithm for adults with primary hyperparathyroidism 190 × 275 mm (96 × 96 DPI)

themselves, as they are aware of the skillset available in their own practice setting.

Recommendation 4.1: Patients with symptomatic PHPT who are good operative candidates, based on an assessment of operative risk and life expectancy, should be referred for surgery.

The definition of symptomatic PHPT is unclear, and detection of symptoms often depends on skilled history taking, as many patients disregard subtle symptoms as part of normal ageing. The most obvious symptoms of PHPT arise from complications of kidney stones (pain, obstruction), osteoporosis (fragility fractures) and acute hypercalcaemic illness (nausea, vomiting, dehydration and confusion) (Table 1).

Some patients experience marked musculoskeletal or neurocognitive symptoms without another evident cause and have sometimes been previously diagnosed with fibromyalgia or chronic fatigue. Symptomatic patients often experience demonstrable improvement in symptoms following curative parathyroidectomy.[33]

Recommendation 4.2: Parathyroidectomy is indicated in patients with PHPT who are at increased risk of fracture, based on current bone density and fracture history.

Patients with PHPT and osteoporosis benefit from parathyroidectomy. Primary hyperparathyroidism causes a progressive decrease in BMD,[61] most pronounced at cortical bone sites, such as the distal radius, but also in sites rich in trabecular bone such as the vertebral column.

Parathyroidectomy improves BMD and may reduce fracture rate, even for patients with normal or osteopenic BMD values.[23] There is observational evidence[25,26,61] that surgery for PHPT decreases fracture risk compared with bisphosphonate treatment or observation. Patients with high fracture risk should be considered for osteoporotic drug therapy, even if submitted to parathyroidectomy.

Recommendation 4.3: Parathyroidectomy is indicated for patients with PHPT and evidence of renal tract calcification including nephrolithiasis and nephrocalcinosis.

TABLE 1 Symptoms attributable to primary hyperparathyroidism

Musculoskeletal	Neurocognitive	Gastrointestinal, Urinary, General
Muscle pain	'Brain fog'	Constipation
Muscle weakness	Anxiety or depression	Nausea
Bone pain	Irritable mood	Reflux
Fragility fracture	Poor/disrupted sleep	Increased thirst
Arthralgia	Confusion	Increased urination
'Fibromyalgia'	Lack of motivation	Vague abdominal pain
	Poor memory/ concentration	Itchy skin
	Fatigue	Renal colic
	Decreased libido	

Parathyroidectomy reduces development of new kidney stones by at least 8%,[62] but probably much more.[63] Although impaired glomerular filtration rate and nephrocalcinosis do not resolve, surgery may prevent a further decline in glomerular filtration rate.

Recommendation 4.4: Parathyroidectomy may be considered for patients with musculoskeletal symptoms attributable to PHPT.[64,65]

There is some evidence that nonspecific musculoskeletal pain may respond to parathyroidectomy. However, musculoskeletal symptoms are multifactorial and nonspecific, and we note that it is, a priori very difficult to define which musculoskeletal symptoms could be attributed to PHPT.

Recommendation 4.5: Parathyroidectomy is recommended for patients with neurocognitive and/or neuropsychiatric symptoms attributable to PHPT

Patients with PHPT often suffer neurocognitive and neuropsychiatric symptoms. Several trials have demonstrated improvement in symptoms following surgery—in comparison with observation.[59,60,66–68]

Experienced clinicians must advise patients on the probability that their symptoms may reasonably be attributed to PHPT. However, the association of nonspecific symptoms with PHPT in any one patient may become clear only in retrospect after surgery.

Recommendation 4.6: Patients with mildly elevated levels of calcium should be assessed and managed in a similar manner to those with more severe hypercalcaemia

There is no clear evidence to support a specific degree of hypercalcaemia, above which surgery should be indicated. Some patients with normal calcium may in fact have elevated ionised calcium levels in the setting of low albumin secondary to other pathology. Furthermore, there is evidence that BMD decline in PHPT occurs independent of degree of hypercalcaemia.[61] Parathyroidectomy should be considered for any symptomatic patient with PHPT who is otherwise fit for surgery.

Although there is no strong correlation between severity of hypercalcaemia and PHPT symptoms and end-organ effects, patients with higher calcium levels may be more likely to achieve symptomatic benefit after surgery. Therefore, serum calcium persistently above the reference range or a single calcium >0.25 mmol/L above the local reference range swings the risk/benefit ratio further towards surgery. This cut-off is a relatively arbitrary point on a continuum, recommended based on expert consensus[69] and subject to debate.

4.1.5 | What is the management of asymptomatic hyperparathyroidism?

Asymptomatic patients with PHPT, by definition, have no overt clinical signs. This however does not mean that the traditional target organs are not affected. Many asymptomatic patients do not experience disease progression, defined by worsening hypercalcemia, hypercalciuria, kidney stones or bone disease. These patients should be informed of the risks and benefits of observation versus surgery. Some asymptomatic patients will experience disease progression and then benefit from surgical intervention.

Identifying asymptomatic patients who are likely to progress and those for whom surgical intervention is beneficial is a priority for future studies (Table 2). Until more rigorous evidence (currently lacking in aspects of asymptomatic HPT) is available from controlled clinical trials, management requires discussion between the clinician and patient, to ascertain risks and benefits of treatment.

Recommendation 5.1: Before considering observation rather than surgery, asymptomatic PHPT patients should be assessed for evidence of end-organ complications, including loss of bone mineral density, vertebral compression fractures, or nephrolithiasis. The finding of such complications would be an indication to undergo surgery in patients with reasonable life expectancy.

Despite the absence of symptoms, PHPT may lead to the development of direct end-organ complications over time. These silent complications may progress without adequate correction of the

TABLE 2 Guidelines for the management of 'asymptomatic' primary hyperparathyroidism

Strongly advise surgery	Advise/consider surgery	Nonsurgical management
• Life expectancy >10 years • AND • Low anaesthetic risk • WITH • Osteoporosis or • Fragility fracture or • Vertebral compression or • Renal tract calculus or • Corrected calcium >2.75 mmol	• Life expectancy >5–10 years • AND • Low anaesthetic risk • WITH • Osteopenia or • Significant[a] bone loss over time or • Raised urine calcium excretion or • Patient preference	• Life expectancy <5 years • OR • Prohibitive anaesthetic risk • OR • Hostile neck (e.g., previous neck surgery, irradiation, morbid obesity)

[a]A significant reduction is defined by a reduction that is greater than the least significant change as defined by the International Society for Clinical Densitometry.

underlying condition. Studies report that up to 30% of patients with asymptomatic PHPT may develop complications over 10–15 years of follow-up,[70] and adequate assessment of end-organ disease at initial presentation and at subsequent intervals is necessary.

Recommendation 5.2: Patients with asymptomatic PHPT without end-organ damage who are fit to tolerate anaesthesia, and who have a life expectancy >10 years, should be informed of the benefits and risks of surgical treatment versus observation.

Previous guidelines have specified age <50 years as an indication for surgery in PHPT, given the likelihood of disease progression within a person's lifetime. Patients with asymptomatic hyperparathyroidism demonstrate a gradual but significant decline in bone density over a 10-year period, and an increased risk of fragility fracture.[71] The longer the life expectancy, the more onerous and expensive the long-term monitoring and the greater the risk of progression.[72]

These guidelines propose an individualised assessment of a person's likely long-term benefits of surgery, in considering a life expectancy >10 years from time of diagnosis. Please see Figure 1 for an algorithm of the suggested approach. For most patients, parathyroidectomy is a relatively minor operation when performed by experienced surgeon. In experienced hands, the risk of postoperative complication in patients undergoing parathyroidectomy is <1%. In experienced surgical hands, the hospital stay is brief and the recovery to normal activity rapid. Risks of surgery in less experienced hands are likely to be greater, and should be balanced against long-term observation.

In a US health care setting,[73] the cost-effectiveness and utility of surgery is high compared to long-term observation and monitoring. Similar economic data is currently not available in Australia and New Zealand, but is needed. Surgical risks should be balanced with the risks of long-term end-organ disease in patients with PHPT, which may approach 30% even in those with asymptomatic disease at baseline.

Recommendation 5.3: Parathyroidectomy should be considered in patients who develop end-organ complications (progression of bone loss, development of fracture, kidney stones, worsening renal function) or if the serum calcium >0.25 mmol/L above the local reference range, unless the surgical or anaesthetic risk is unfavourable.

Worsening symptoms, biochemical abnormalities, increased urinary calcium excretion and a significant and clinically relevant decrease in BMD on follow-up should all lead to reappraisal and consideration of surgery (Table 3).

Patients who decline surgery or who are not considered surgical candidates may be considered for medical therapy such as anti-resorptive therapies to treat osteoporosis, or the use of calcimimetic such as cinacalcet for the management of symptomatic hypercalcaemia. Denosumab may also be considered as a suitable alternative to bisphosphonates in this setting.[74,75] These treatments are not as effective as surgery in normalising calcium and reversing end-organ complications of PHPT.

Although osteoporosis is an indication for surgery, patients with osteoporosis who do not have surgery should have appropriate bone-preserving treatment in the absence of contraindications. Several studies have demonstrated the efficacy of bisphosphonates in improving BMD in this cohort.[66–70] There is recent emerging evidence suggesting that denosumab is also effective in improving BMD in patients with primary hyperparathyroidism.[71] It is important to ensure that these patients are vitamin D replete (i.e., vitamin D level >50 nmol/L). Patients with osteoporosis undergoing parathyroidectomy may also require anti-resorptive therapy to further reduce their risk of fracture, following recommendations for anti-resorptive therapy for the general population.

TABLE 3 Indications for switching to parathyroid surgery during monitoring of asymptomatic primary hyperparathyroidism

System assessment	Indication to consider surgery
Bone	A. T-score ≤ −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius
	B. Significant reduction in BMD[a]
	C. Vertebral fracture by X-ray, CT, MRI or VFA
Serum calcium	Corrected serum calcium >2.75 mmol/L
Renal	A. Clinical or radiological evidence of a kidney stone.
	B. Elevated urinary calcium excretion
	C. Deteriorating renal function, no other explanation. eGFR now <60 ml/min

[a]A significant reduction is defined by a reduction on repeat scanning that is greater than the least significant change as defined by the International Society for Clinical Densitometry.

Recommendation 5.4: Multidisciplinary assessment and input is recommended when the diagnosis is difficult or nuanced and/or the risk/benefit is not obvious.

In a subset of patients, the biochemical diagnosis may not be straightforward, and likelihood of benefit from surgery may be unclear. In these situations, cases should be reviewed by a multidisciplinary team, and a consensus management plan should be formulated.

Recommendation 5.5: Patients who are monitored or managed medically should undergo annual evaluation.

Regular evaluation of patients for whom observation is jointly decided should be undertaken, including:

- Annual reassessment of biochemistry including serum corrected calcium and/or ionised calcium, Vitamin D, renal function, urinary calcium excretion, symptom assessment, and interval history of new fracture, or renal stones.
- DXA scan at 2 years, with subsequent individualised surveillance frequency. Ideally, the repeat DXA would be performed on the same machine, with the least significant change (LSC) at the facility as well as significant change in BMD between the current and previous DXA reported. Screening for kidney stones with ultrasound may be considered every 5 years.

Recommendation 5.6: Parathyroidectomy for PHPT is not recommended when the risks of surgery or anaesthesia outweigh the anticipated benefits of cure.

In patients who do not meet indications for surgical intervention, refuse surgery, or are considered high risk, medical intervention may attempt to mitigate specific sequelae.[3]

A schematic representation of recommendations favouring medical management/observation versus surgery for different symptomatology is available in Figure 2.

4.2 | SECTION B: SPECIAL CONSIDERATIONS

4.2.1 | How does the management of hyperparathyroidism in pregnancy differ?

Primary hyperparathyroidism is rare in pregnancy, with clinical knowledge restricted to isolated case reports and a few retrospective studies. Maternal complications of hyperparathyroidism in pregnancy include hyperemesis, nephrolithiasis, hypercalcaemic crisis, hypertension, pre-eclampsia and eclampsia. Foetal complications include intrauterine growth restriction (IUGR), premature delivery, stillbirth and neonatal tetany.[76]

Recommendation 6.1: If PHPT is diagnosed in a woman of childbearing age, curative surgery is recommended before pregnancy where possible.

In pregnant women, mild cases (serum calcium <2.7 mmol/L) may be managed non-operatively. Medical management in pregnancy includes adequate hydration, avoidance of exacerbating factors including calcium supplementation, and monitoring of the calcium level, and maternal and fetal wellbeing. Corrected calcium may be unreliable given the decrease in albumin in pregnancy, and ionised calcium levels are preferred.

More severe cases generally should be operated, preferably in the second trimester. Ultrasonography is the preferred modality for localising the parathyroid lesion, although foetal radiation exposure is minimal with parathyroid CT. A medical physicist should be consulted regarding radiation risk. One recent guideline recommended parathyroidectomy in the second trimester if the ionised calcium was 0.12 mmol/L above the upper limit of normal.[77] Following successful surgery, provided residual parathyroid function is retained, serum calcium levels normalise. In experienced hands, the risk of maternal complications including laryngeal nerve palsy and postoperative hypocalcaemia is low. A child born to a hypercalcaemic mother should be managed as high risk, with particular attention paid to avoid neonatal hypocalcaemia and tetany.

In pregnancy, the safety of cinacalcet is unknown and not recommended. Bisphosphonates and denosumab are contraindicated.

Recommendation 6.2: When severe PHPT is diagnosed in pregnancy, parathyroidectomy is recommended in the second trimester, with ultrasound being the preferred localisation study.

Management of hyperparathyroidism in pregnancy requires a multidisciplinary team with endocrinology, surgical and obstetric expertise. Although general guiding principles exist, treatment is individualised according to the degree hypercalcemia, gestation and maternal/fetal factors.

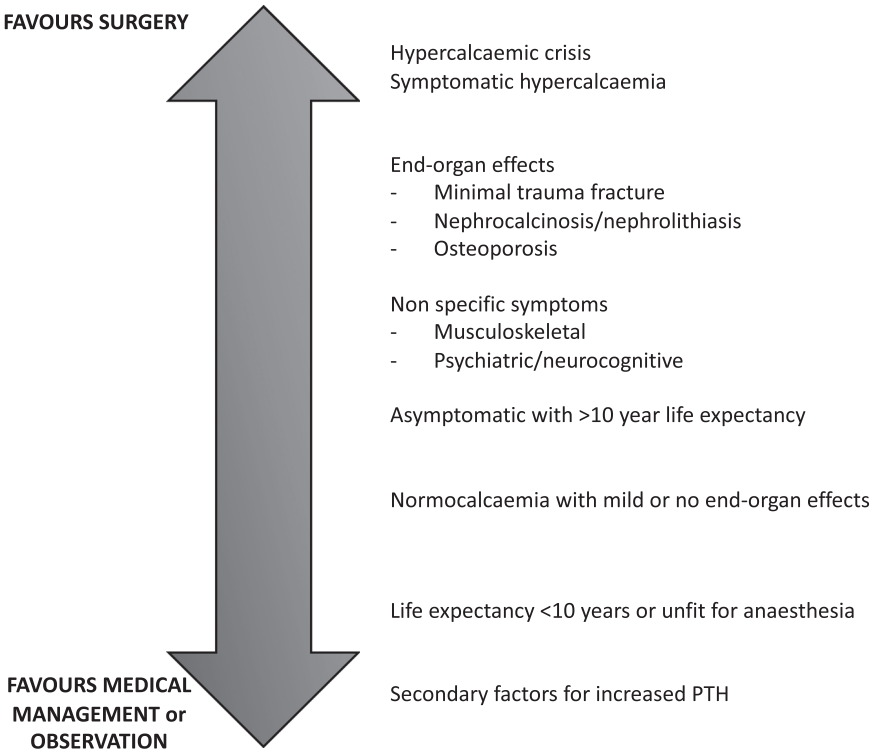

FIGURE 2 Recommendations favouring medical management/observation versus surgery for different symptomatology

4.2.2 | When should parathyroid carcinoma be suspected?

Recommendation 7.1: In a patient with PHPT, a palpable neck mass, severely elevated calcium or PTH, and large tumour size are features suspicious for parathyroid carcinoma and should prompt careful evaluation.

Parathyroid carcinoma is uncommon (approximately 0.5% of all PHPT cases).[78–82] Awareness aids diagnosis, treatment planning and outcomes.

Parathyroid carcinoma mimics benign PHPT and a definitive preoperative diagnosis is unusual.[81] Patients present incidentally or with hypercalcemia and there is a strong association with Hyperparathyroidism Jaw Tumour Syndrome (HPT-JT) caused by germline *CDC73* mutations.[81,83,84] In HPT-JT the lifetime risk of parathyroid carcinoma may be as high as 38%.[85] Up to 25% of parathyroid carcinoma patients may have germline *CDC73* mutations.[81,83,84] There is no clear association between MEN1/2 and parathyroid carcinoma.[84]

Severe hypercalcemia (>3.0 mmol/L) and/or a markedly elevated PTH (>300 pmol/L) are more common in parathyroid carcinoma. Symptomatic hypercalcemia causing bone pain or renal calculi is therefore more common.[86,87] A palpable mass may be present in 50%[88,89] and larger tumours (>3 cm) are also more frequent.[90,91] Sonographic size, invasion and elevated PTH are independent predictors of disease.[92]

When preoperative suspicion of parathyroid carcinoma is high or when encountered at operation, consultation from an experienced endocrine surgery unit should be obtained. Surgical management of parathyroid carcinoma is detailed in Chapter 8, Part II of this position statement.

4.2.3 | When should familial hyperparathyroidism be suspected and what is the role for genetic testing?

Genetic testing for heritable germline mutations is valuable in patients with PTH-dependent hypercalcaemia and features suggestive of either a PHPT predisposition syndrome or FHH. In the case of the PHPT predisposition syndromes, identifying a causative mutation guides operative planning and surveillance for other relevant tumours, cascade testing of relatives, and reproductive planning. For example, identifying an *MEN1* mutation in a patient with otherwise seemingly isolated PHPT would alter surgical planning, trigger surveillance for associated neoplasms, cascade testing of relatives, and discussion of reproductive planning including the option of IVF with pre-implantation genetic testing and transfer of only unaffected embryos. In contrast, genetic testing for FHH is used to confirm a clinical diagnosis and avoid unwarranted surgery. Genetic testing in suspected FHH may also facilitate cascade testing of hypercalcaemic relatives and aid family planning in relation to the risk of neonatal severe hyperparathyroidism. Figure 3.

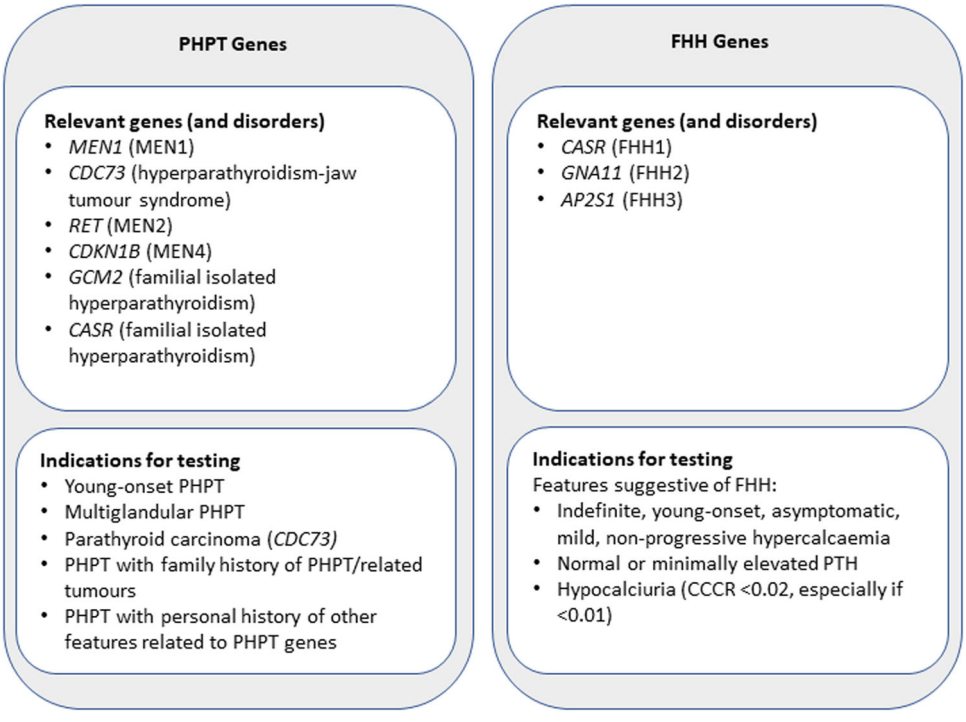

FIGURE 3 Summary of genetic testing approach in suspected familial PTH-dependent hypercal caemia*

Recommendation 8.1: Genetic testing is recommended in patients with PHPT with young-onset or multi-gland disease, parathyroid carcinoma, a family history of PHPT and/or related tumours, and/or a personal history of other features related to PHPT predisposition syndromes. Genetic testing should also be considered in hypercalcaemic patients with features suggestive of FHH.

Genetic testing of cancer and/or tumour predisposition genes is indicated when the chance of testing positive for a clinically actionable germline mutation is ≥10%.[93] Accordingly, genetic testing of PHPT genes is recommended in patients with the following risk factors, with the approximate yield of genetic testing indicated where relevant:

- young-onset PHPT (e.g., ≤45 yo, ~10% yield);[94]
- multiglandular PHPT (~25%);[95]
- parathyroid carcinoma (~20% positive for germline *CDC73* mutations);[96]
- PHPT with a family history of PHPT and/or related tumours (20%–60%);[97,98] or
- a personal history of other features related to PHPT predisposition genes (i.e., *MEN1*: pituitary and pancreatic tumours, angiofibromas, collagenomas and lipomas; *CDC73*: jaw, uterine and renal tumours; *RET*: medullary thyroid cancer, phaeochromocytoma and cutaneous lichen amyloidosis).[99]

Genetic testing of FHH genes is less prescriptive and may be considered whenever a diagnosis of FHH is considered possible or likely. Features raising suspicion for FHH in the setting of PTH-dependent hypercalcaemia include:

- Young-onset, asymptomatic, mild and nonprogressive hypercalcaemia;
- Normal or minimally elevated PTH; and
- Unexplained hypocalciuria, defined by CCCR < 0.02 (especially if <0.01).[1,4,100,101]

Overall, positive family history and—for FHH—CCCR < 0.01 are the strongest individual predictors of testing positive for a heritable cause of hyperparathyroidism.[102]

Recommendation 8.2: Genes selected for investigation should be determined according to testing indication. *MEN1*, *CDC73*, *RET*, *CDKN1B*, *GCM2* and *CASR* should be assessed if a PHPT predisposition syndrome is suspected, whereas *CASR*, *AP2S1* and *GNA11* should be assessed in suspected FHH.

MEN1, *CDC73* and *RET* are well-known PHPT predisposition genes associated with PHPT and other neoplasms.[100] *CDKN1B* is associated with MEN4, a phenotype akin to MEN1 albeit much rarer.[100] *GCM2* is an emerging PHPT predisposition gene associated with isolated PHPT.[97]

FHH is due to mutations in *CASR* in two-thirds of cases overall,[100] although the probability of finding a *CASR* mutation is likely much higher in those with hypocalciuric hypercalcaemia and a positive family history. FHH is rarely due to mutations in *AP2S1* or *GNA11*.[100]

Although *CASR* is best known for its role in FHH, loss-of-function *CASR* variants may also rarely produce a familial PHPT phenotype,[103,104] and thus this gene may also be considered a PHPT gene. Whether a patient with PTH-dependent hypercalcaemia and a *CASR* mutation is considered to have PHPT or FHH should take into account the patient's overall clinical picture.

Depending on clinical and biochemical features, a patient may meet criteria for testing of PHPT genes, FHH genes, or both PHPT and FHH genes.

Next-generation sequencing allows simultaneous testing of all relevant genes. Nonetheless, restricting mutation analysis to only those genes directly corresponding to a patient's phenotype (PHPT vs. FHH) minimises the burden of variants of uncertain significance. For example, finding a variant of uncertain significance in *AP2S1* in a patient with unequivocal parathyroid autonomy may cause unnecessary anxiety in the patient and hesitancy in treating clinicians not familiar with the meaning of variants of uncertain significance. On the other hand, a large next generation sequencing study of 121 patients by Mariathasan et al reported cases of FHH being molecularly diagnosed despite a clinical diagnosis of PHPT, and vice versa, arguing for all hyperparathyroidism genes to be tested in patients who qualify for genetic testing.[102] The optimal approach to gene selection may depend on the extent of data available for pre-test phenotyping; future research may help to clarify this.

Recommendation 8.3: Genetic testing should be ordered in the context of pretest and posttest counselling, and with consideration of testing methodologies.

Depending on local frameworks, genetic testing may be performed by a dedicated genetics service including genetic counsellors or a treating clinician with genetics expertise. Pre-test counselling should address the utility, process and risks of genetic testing, including the possibilities of discovering previously unknown health risks, revealing non-paternity and insurance implications.

Genetic testing performed preoperatively may guide surgical management. Nonetheless, genetic testing remains valuable in postoperative patients meeting testing criteria as finding a causative mutation may influence ongoing management and surveillance. Testing may involve direct gene sequencing or next-generation sequencing. Dedicated assessment for copy number variants—for example, by multiplex ligation-dependent probe amplification—should be considered specifically for *MEN1* and *CDC73* as deletions in these genes account for 4% and 35% of affected cases, respectively.[105,106]

Posttest counselling should initiate cascade testing of relatives if a mutation is detected. In FHH, at-risk relatives can be screened with a serum calcium level with genetic testing restricted to hypercalcaemic relatives. Serum calcium checks should also be considered in reproductive partners of individuals with *CASR* mutations because of the 1 in 4 risk of neonatal severe hyperparathyroidism due to biallelic *CASR* inactivation in offspring when both parents carry a *CASR* mutation.

If genetic testing is negative but the clinical context remains suspicious for a familial PHPT syndrome or FHH, updated genetic

testing should be offered at a future time as genetic technologies and our understanding of genetic pathogenesis improve.

5 | CONCLUSION

This collaboration between ESA, ANZES, and ANZBMS has been systematically approached, to provide contemporary evidence-informed clinical consensus recommendations to guide assessment and management of PHPT in adults. While the ADAPTE is a validated and evidence-based approach to guideline evaluation, there was considerable authorship overlap among the 12 guidelines included, and many of these guidelines predominantly pertained to the management of asymptomatic PHPT. This position statement promotes safe, best practice management of adults with PHPT and is to be considered as a broad guide for approaching the assessment and medical management of these patients.

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SUPPORTING INFORMATION

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