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NARRATIVE REVIEW OPEN ACCESS

Primary Hyperparathyroidism in Adults: Recent Developments in Diagnosis and Management

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ABSTRACT

Primary hyperparathyroidism has a prevalence of around 1% in the general population. Diagnosis requires biochemical testing of serum (for calcium and parathyroid hormone) and urine (for calcium excretion), as well as wider screening for complications including osteoporosis, renal disease, abdominal symptoms and neuropsychiatric disturbance. In selected individuals, genetic testing is a key consideration because up to 10% have hereditary primary hyperparathyroidism. Surgery is curative, with a minimally invasive approach preferred after identifying the abnormal parathyroid glands on preoperative imaging. Uncertainty surrounds the diagnosis of non-classical manifestations of primary hyperparathyroidism, preoperative imaging algorithms and management pathways in normocalcaemic primary hyperparathyroidism.

JEL Classification: Endocrine system diseases

1 | Introduction

Primary hyperparathyroidism (PHPT) is an endocrine condition characterised by loss of the normal feedback suppression of serum calcium concentration on the synthesis and secretion of parathyroid hormone (PTH). In most cases (80%–90%), autonomous production of PTH originates from a single adenoma arising from one of the four parathyroid glands; less commonly, there may be multiple affected glands or, extremely rarely, parathyroid carcinoma [1].

Over the past decade, important insights have been gleaned into the epidemiology and genetic landscape of PHPT with new Australian and New Zealand and international consensus guidelines (Table S1) and World Health Organization (WHO) classification of histology [2–6]. This narrative review aims to summarise existing and novel knowledge related to the pathophysiology, assessment and management of PHPT for clinicians, with a focus on historically important and recently published articles and guidelines.

2 | Search Strategy

We searched the PubMed online database from 1 April to 1 September 2025 to identify English-language articles published between September 1970 and August 2025. We used the search terms 'hyperparathyroidism' and 'parathyroid' combined with relevant terms—such as 'incidence', 'genetics', 'osteoporosis', 'parathyroidectomy', 'imaging' and 'normocalcaemic'—using the 'and' Boolean operator between search terms. Among the identified references, we prioritised historically important and most recently published articles and recent evaluation and management guidelines.

3 | Incidence of PHPT

The incidence of PHPT is estimated to be between 16 and 50 cases per 100,000 person-years [7], with an overall prevalence around 1% [8]. The range in incidence reflects global disparities in access to routine biochemical testing (as well as healthcare generally) in addition to differences in population demographics [9]. Sharp increases in incidence in high-income countries were noted after the introduction of widespread serum calcium measurement in the 1970s and screening of individuals with osteoporosis in the 2000s [10]. The incidence of PHPT increases with age and is higher in black and white people than in those of Asian or Hispanic ethnicities [9]. Higher incidence in women—which is almost three times that in men, peaking at age 70–79 years at 27 cases per 10,000 person-years [8]—is postulated to relate to oestrogen receptor signalling [11].

There are minimal published epidemiological data in the Australian population [12]; in particular, no study has focussed on Aboriginal or Torres Strait Islander people. Using data from Medicare billing (reflecting outpatients and private hospitals) combined with MyHospitals.api (public hospitals), we estimate an incidence of 51 cases per 100,000 population, based on 4219 parathyroidectomies performed in 2023–2024 and about 30% of individuals with PHPT requiring surgical management [10]—noting this figure is likely underestimated, with current evidence-based guidelines expanding the percentage of PHPT individuals who should be referred for surgery.

In addition to age, genetic drivers of parathyroid tumorigenesis, female sex and ethnicity, several risk factors have been identified for the development of PHPT. Exposure to ionising radiation including radioactive iodine, particularly in childhood, is associated with PHPT [13, 14]. Social deprivation is associated with higher incidence of PHPT as well as lower rates of surgical management [15]. Chronic lithium use decreases the sensitivity of the parathyroid glands to calcium and typically leads to multiglandular disease rather than a single adenoma. A variety of endocrine-disrupting chemicals have been detected in parathyroid adenomas, but their relationship with PHPT is as yet undefined [16].

The association between chronic vitamin D deficiency and the development of PHPT is incompletely understood. It is possible that inadequate vitamin D stores drive secondary hyperparathyroidism, eventually leading to parathyroid hyperplasia and autonomous production of PTH [17]. However, as PTH stimulates the conversion of 25-hydroxyvitamin D to 1,25dihydroxyvitamin D, over time, depletion of 25-hydroxyvitamin D may occur.

4 | Diagnosis of PHPT

Serum calcium should be measured in patients with any potential clinical feature of PHPT (Figure 1) and in those receiving lithium or are older than 40 years who are undergoing thyroid surgery [2]. An abnormal serum calcium concentration warrants PTH measurement with modern assays that are more specific for active forms of circulating PTH, rather than inactive fragments or PTH-related peptide (PTHrP). In Australia, the majority of PHPT cases are now identified on routine biochemical testing or due to non-specific symptoms such as fatigue.

In classical PHPT, the serum calcium concentration (ionised and/or corrected for serum albumin) is elevated with an elevated or inappropriately normal serum PTH concentration. Other common biochemical abnormalities include a low serum phosphate, elevated alkaline phosphatase (and other bone turnover markers), low 25-hydroxyvitamin D and elevated 1,25-dihydroxyvitamin D concentration. In the setting of advanced kidney disease, tertiary hyperparathyroidism rather than PHPT should be considered. This typically develops after a prolonged period of secondary hyperparathyroidism with subsequent kidney replacement therapy (either dialysis or kidney transplantation) and is often associated with hyperphosphataemia, low 1,25-dihydroxyvitamin D concentration and multiple gland disease [18].

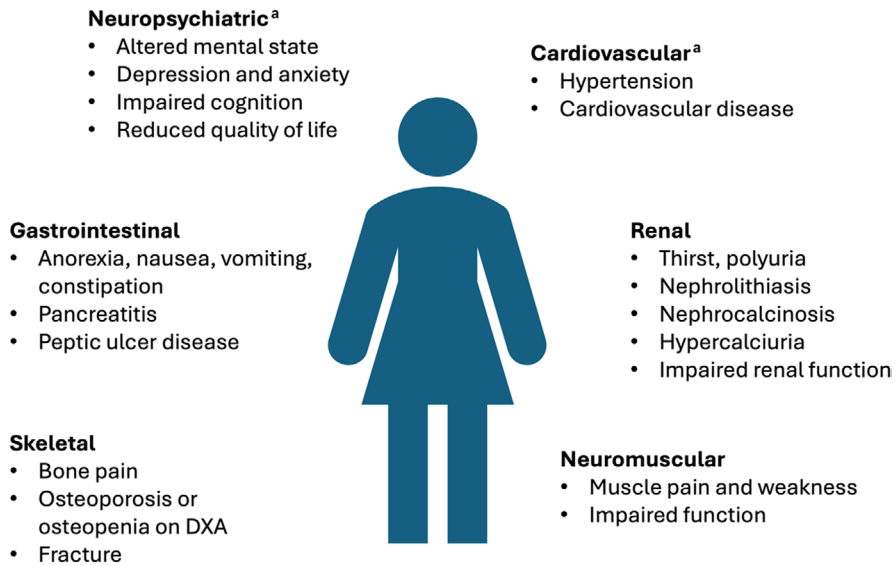

FIGURE 1 | Clinical features of primary hyperparathyroidism. DXA, dual-energy x-ray absorptiometry. [a]Non-classical symptoms.

PHPT must be distinguished from the much rarer condition of familial hypocalciuric hypercalcaemia (FHH), which has a similar serum biochemical profile but with lifelong elevated calcium concentration. This requires calculation of the fractional excretion of calcium, traditionally using a 24-h urine collection, although a spot fasting urine sample may suffice. Urine calcium measurements are influenced by pregnancy, chronic kidney disease, vitamin D deficiency, lithium and thiazide diuretics. Previous serum biochemistry and family history (FHH is autosomal dominantly inherited) may provide useful information, but, ultimately, genetic testing may be required [17]. People with FHH typically have mild asymptomatic hypercalcaemia and medical treatment is not required; patient education is important to avoid unnecessary future intervention.

5 | Further Evaluation

PHPT may be symptomatic or asymptomatic and present with or without target organ involvement [19]. Chronic elevation of PTH may lead to symptomatic hypercalcaemia, osteoporosis (particularly at cortical bone-rich sites such as the distal radius), renal complications, abdominal symptoms and neuropsychiatric disturbance. Classical features include 'brain fog', fatigue, muscle weakness, bone pain, fractures, renal calculi, nephrocalcinosis, polyuria, polydipsia, anorexia, constipation, peptic ulcer disease, pancreatitis and altered mental state [17, 20]. Severe bony complication, such as brown tumours and osteitis fibrosa cystica, are now seldom seen in Australia due to earlier diagnoses. PHPT has been associated with increased mortality rates in some studies [12, 21].

Baseline assessment for PHPT-associated complications includes renal imaging (ultrasound or computed tomography scan), 24-h urine calcium excretion, bone density measurement (dual-energy x-ray absorptiometry [DXA] including radius) and thoracolumbar x-ray [20]. Urine calcium excretion is considered elevated if greater than 6.25 mmol/day (> 250 mg/day) for women and 7.5 mmol/day (> 300 mg/day) for men [6].

PHPT is increasingly recognised as a cardiovascular risk factor, with large cohort studies reporting high prevalence rates of hypertension [22, 23]. PHPT-driven hypercalcaemia may result in arterial calcification and alter renin–angiotensin–aldosterone system signalling, leading to premature atherosclerosis. A full cardiovascular work-up is currently not guideline-recommended; however, measuring blood pressure is a routine part of most outpatient appointments.

6 | Referring Patients for Surgery

Recent Australian guidelines recommend treatment for the following indications [2]:

- symptoms (Figure 1);
- osteoporosis—radiological (bone density) or clinical (minimal trauma fracture);
- renal complications—nephrolithiasis, nephrocalcinosis, hypercalciuria, deteriorating renal function or glomerular filtration rate below 60 mL/min/1.73 m^2 in the absence of another explanation; and
- asymptomatic and aged < 50 years (consider if aged > 50 years, provided life expectancy is > 10 years).

Surgery is the only definitive treatment for PHPT. Successful surgery for PHPT improves bone health and prevents further decline in renal function although the effects on cardiovascular disease and neurocognitive symptoms is unclear [1, 24, 25]. Inconsistent effects on mortality have been reported [12, 26, 27].

Commonly performed surgical approaches include a targeted, minimally invasive parathyroidectomy or a bilateral neck exploration [28]. Both can achieve cure rates above 95% [28]. Potential complications are rare but include bleeding, infection, damage to the recurrent laryngeal nerve and hypoparathyroidism. Compared with the non-targeted approach of bilateral neck exploration, minimally invasive parathyroidectomy is associated with a smaller incision, shorter duration of operation, increased patient satisfaction and lower risk of complications. It is therefore the preferred approach for most cases of PHPT, provided successful preoperative localisation [29]. In multiple endocrine neoplasia type 1 (MEN1) syndrome, the preferred operation is bilateral neck exploration with three or three and a half gland parathyroidectomy (due to high recurrence rates of PHPT) combined with transcervical thymectomy to capture ectopic parathyroid tissue—this may also reduce the risk of thymic neuroendocrine tumours [30].

Substantial published evidence supports high volume surgeons achieving better outcomes [28]. Adequate parathyroid surgical volumes are poorly defined—consistently > 15 cases per year is likely sufficient for simple cases, or > 50 cases per year for complex cases (e.g., persistent/recurrent PHPT) [3, 19].

A variety of intraoperative adjuncts such as frozen sections, intraoperative PTH measurement, parathyroid aspiration (for measurement of PTH), radio-guidance, methylene blue, intraoperative ultrasound, jugular venous sampling of PTH and parathyroid fluorescence have been studied. Currently, none have consistently demonstrated benefit or cost effectiveness and are not widely available in Australia [3]. Neuromonitoring of the recurrent laryngeal nerve should be considered during repeat operations due to higher risk of injury.

6.1 | Histology

An updated WHO classification of parathyroid tumours published in 2022 reflects an increased understanding of the pathogenesis of parathyroid disease [4]. It emphasised the importance of molecular immunohistochemistry and genetic testing. For example, loss of normal nucleolar parafibromin immunoreactivity suggests an underlying germline or somatic *CDC73* mutation and greater risk of parathyroid carcinoma. The term 'hyperplasia' was no longer recommended in the setting of PHPT, as affected glands are usually composed of multiple clonal neoplastic proliferations. A new term, 'atypical parathyroid tumour', was introduced to classify

tumours of uncertain malignant potential that warrant long-term follow-up. These tumours demonstrate atypical cytological and architectural features that are worrisome for parathyroid carcinoma, but lack capsular, vascular or perineural invasion or invasion into adjacent structures or metastases.

7 | Localisation Studies to Perform Before Surgery

7.1 | Imaging

Localising imaging to identify the responsible parathyroid glands does not affect the diagnosis of PHPT and should not influence the decision to consider surgery. However, it can affect the decision to operate; for example, by enabling a minimally invasive parathyroidectomy to be performed in a high-risk patient who may be unsuitable for a more complex bilateral neck exploration. Imaging may identify ectopic parathyroid glands in the mediastinum, which requires a thoracoscopic approach. Several modalities are available, with distinct advantages and disadvantages (Table 1). Some controversy exists around the exact algorithm on how they should be employed (Figure 2). Due to these nuances, it is recommended that imaging is requested by a parathyroid specialist (an endocrinologist or surgeon) and performed at experienced centres. No investigation is 100% sensitive; therefore, patients with negative imaging who meet criteria for surgery should still be reviewed for operative management.

7.2 | Venous Sampling

Catheterisation of the parathyroid venous drainage pathways can facilitate localisation of PTH secretion [41], but this complex and invasive procedure is reserved for cases where imaging is negative or equivocal. It should only be performed at expert parathyroid centres.

8 | Perioperative Advice for Patients

Preoperatively, it is important to maintain adequate hydration. There is no evidence for restriction in dietary calcium intake if within normal daily recommendations. Similarly, replacing deficient vitamin D does not worsen PHPT and may reduce postoperative hypocalcaemia [42]. Patients with moderate (3.0–3.5 mmol/L) or severe (> 3.5 mmol/L) hypercalcaemia generally require admission for parenteral hydration, an antiresorptive and/or cinacalcet to achieve an appropriate calcium concentration for anaesthesia [43]. The exact threshold for anaesthetic safety is poorly defined, although in our experience a serum albumin-adjusted calcium of < 3.0 mmol/L has not raised concern.

Postoperatively, biochemistry should be measured within 24 h of surgery to ensure an appropriate fall in PTH and confirm eucalcaemia. Hypocalcaemia can be due to hypoparathyroidism or hungry bone syndrome. Hypoparathyroidism occurs if multiple glands are removed or devascularised during surgery. Typically, this is associated with a high serum phosphate and low or inappropriately normal PTH. It is usually transient [44]. Hungry bone syndrome occurs with massive transfer of calcium to bone, characterised by a normal or high PTH and low serum phosphate and magnesium. Risk factors include older age, very high preoperative PTH or calcium concentration, large volume parathyroid adenoma, PHPT-related bony disease, elevated bone turnover markers and vitamin D deficiency [45]. The treatment of both conditions requires replacement of calcium (oral or intravenous depending on severity) and calcitriol, with larger doses necessary for hungry bone syndrome. Calcitriol administration for 1 week before surgery may be beneficial although is not currently guideline-recommended [46, 47].

Follow-up after successful surgical management includes:

- serum calcium and vitamin D testing annually, with PTH as clinically indicated [5]; and
- DXA (including radius) 1–2 years postoperatively, with ongoing treatment and surveillance depending on this result.

There is insufficient evidence to recommend monitoring of other PHPT-associated complications [3].

Postoperative cure is commonly defined as eucalcaemia at 6 months after surgery, regardless of PTH concentration [3]. It is not recommended to continue monitoring PTH in the setting of normocalcaemia, as it may remain elevated after successful surgery due to downregulation of the calcium-sensing receptors (CaSRs) on the remaining normal parathyroid glands. Once postoperative cure has been confirmed, long-term follow-up is generally conducted in primary care unless additional considerations are present, such as a genetic cause of PHPT or continuing osteoporosis.

9 | Selecting Patients for Genetic Testing

Recent progress using next generation sequencing has made substantial headway to elucidate the genetic drivers of parathyroid tumorigenesis [11]. Gene variants associated with hyperparathyroidism may occur as somatic or germline variations, although somatic variants do not guide treatment and are not currently part of clinical practice.

Hyperparathyroidism has a hereditary basis in up to 10% of PHPT cases, although not all such cases will have an identifiable germline genetic variant. Conversely, some individuals found to have a germline genetic variant will have a negative family history, which may reflect de novo variants, non-penetrance in relatives with the causative variant or missed diagnosis in relatives.

The genes responsible for hereditary hyperparathyroidism and their corresponding syndromes are *MEN1* (MEN1 syndrome), *RET* (multiple endocrine neoplasia type 2A [MEN2A] syndrome), *CDKN1B* (multiple endocrine neoplasia type 4 [MEN4] syndrome), *CDC73* (hyperparathyroidism-jaw tumour syndrome), and *CASR* and *GCM2* (both producing familial isolated primary hyperparathyroidism) [48].

Germline variants are ideally identified preoperatively, as their presence may modify surgical approach. Indications for genetic

TABLE 1 | Comparison of different preoperative imaging modalities.

Imaging modality	Description	Advantages	Disadvantages	Sensitivity	Radiation exposure
Neck ultrasound	Useful in combination with another test to define the relationship of an identified lesion with the thyroid. A fine-needle aspirate is not required and may cause tumour seeding in the rare case of parathyroid carcinoma. The surgeon may perform their own ultrasound before or during the operation. Normal parathyroid glands are not typically seen on ultrasound.	• Can identify concurrent thyroid pathology requiring operative management at time of parathyroid surgery. • Quick and cheap to perform. No radiation.	• Reliance on operator skill. • Inability to identify very small or ectopic parathyroid glands. • False negatives due to patient body habitus [3].	55%–70% [31–33]	Nil.
[^{99m}Tc]Sestamibi SPECT/CT	In Australia, this usually involves a single isotope ([^{99m}Tc]Sestamibi) with early and late phase imaging combined with low dose SPECT/CT.	• Imaging encompasses a large field of view so can identify ectopic mediastinal lesions. • No intravenous contrast.	• False negatives due to multiglandular disease or adenomas with few oxyphil cells. • May take up to 4 h to perform.	Around 65% [33, 34]	Around 12 mSv, equivalent to about 6 years of background radiation exposure [35, 36].
4DCT	Multiple phase contrast-enhanced CT of the neck—the fourth dimension refers to time. Different washout characteristics of parathyroid adenomas distinguish them from background tissue.	• Shorter imaging time (1 h). • Imaging encompasses a large field of view so can identify ectopic mediastinal lesions. • Good anatomical detail.	• Contrast is problematic for patients with allergies or renal impairment. • Accurate interpretation relies on an experienced radiologist, ideally with feedback from their surgical colleague.	Around 85% [33, 37]	6–28 mSv, depending on patient body habitus and local equipment [35, 36].
[^{18}F]FCH PET/CT	PET using [^{18}F]FCH radiotracer combined with CT. Widely used in Europe as a second- or third-line technique where sestamibi and 4DCT do not localise an abnormal parathyroid gland.	• Quick to perform (around 1 h). • No intravenous contrast.	• In Australia, availability limited to select sites in Perth and Brisbane, although due to the relative stability of [^{18}F]FCH, it has been shipped to Sydney. • Currently, no MBS item number exists, so use is restricted to an externally funded or research setting.	Approaching 95% [34, 38]	6–12 mSv, depending on local imaging protocol and equipment [39].
4DMRI	Multiple phase contrast-enhanced MRI of the neck. It has also been combined with [^{18}F]FCH in research settings to further enhance accuracy.	• Greater soft tissue contrast resolution [35]. • No radiation.	• In Australia, use is restricted by access, cost and interpretive skill.	Small studies in expert centres have reported excellent sensitivity [40].	Nil.

Abbreviations: [^{18}F]FCH, [^{18}F]fluorocholine; 4DCT, four-dimensional computed tomography; CT, computed tomography; MBS, Medicare Benefits Schedule; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

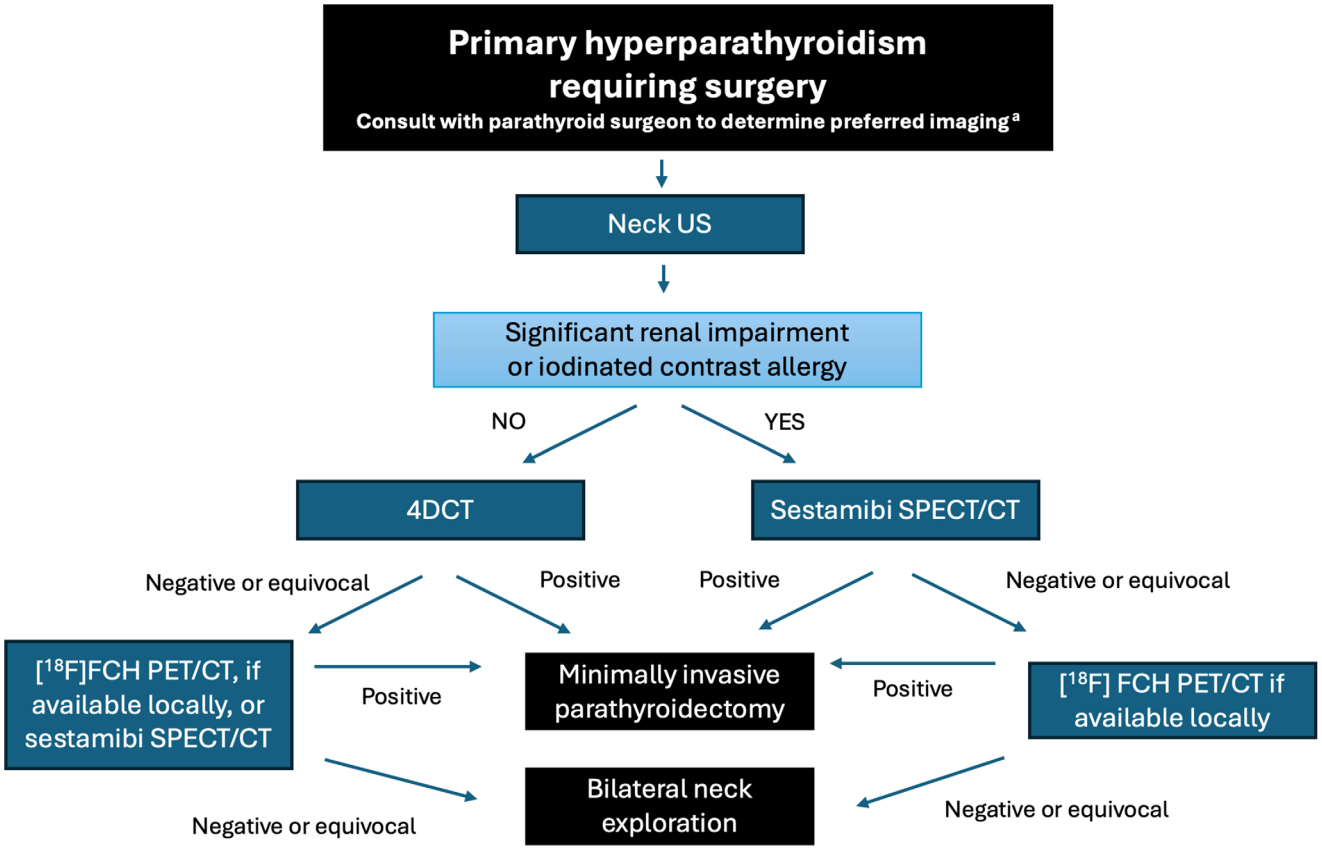

FIGURE 2 | A suggested algorithm of localisation studies. [^{18}F]FCH, [^{18}F]fluorocholine; 4DCT, four-dimensional computed tomography; CT, computed tomography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; US, ultrasound. [a]Depending on local availability and medical imaging expertise, as well as surgeon preference, sestamibi SPECT/CT may be considered first line in all patients, with 4DCT reserved for those with negative or equivocal results. Our preference for patients with clinical suspicion of multiglandular disease (e.g., MEN1 syndrome) or persistent/recurrent disease is first-line [^{18}F]FCH PET/CT, although availability is currently limited.

testing, as detailed below, should be evident before surgery, apart from multiglandular disease, which may only be evident intraoperatively or on histopathology. Even after surgery, genetic testing remains relevant to guide screening for related clinical manifestations, facilitate cascade testing of relatives and guide ongoing surveillance and prognosis (e.g., in people with germline *CDC73* mutations, who have a lifetime risk of parathyroid carcinoma approaching 30% [49]). In people of childbearing age, identification of a germline variant has important reproductive implications.

Genetic testing should be considered in the following groups [50]:

- young-onset PHPT (i.e., by age 40–45 years) [2, 51];
- multiglandular PHPT, either synchronous (presenting simultaneously) or metachronous (persistent or recurrent PHPT after resection of a pathologically abnormal parathyroid gland);
- personal history of other features related to PHPT predisposition genes (e.g., pituitary adenomas; gastric, duodenal or pancreatic neuroendocrine tumours; angiofibromas; collagenomas; and lipomas associated with *MEN1*);
- family history of PHPT and/or related tumours; and
- parathyroid carcinoma, atypical parathyroid adenoma, or typical parathyroid adenoma with absent nuclear parafibromin immunostaining [4].

For a practical guide to genetic testing in PHPT, please see De Sousa et al. [50].

10 | Management of Persistent or Recurrent Disease

Persistent PHPT is defined as a failure to achieve normocalcaemia within 6 months of parathyroidectomy. In contrast, recurrent PHPT refers to recurrence of hypercalcaemia after documentation of normocalcaemia at more than 6 months after parathyroidectomy. Both situations require careful re-evaluation to confirm the diagnosis as potential explanations include

- missed FHH, rather than PHPT;
- PHPT with normal parathyroid glands removed, but abnormal glands left in situ; for example, due to incorrect preoperative localisation;
- PHPT with successful removal of abnormal glands, but residual abnormal glands left in situ; that is, synchronous multiglandular disease;

- PHPT with successful removal of abnormal glands, but new abnormal parathyroid tissue; that is, metachronous multiglandular disease or parathyromatosis (a rare condition where nodules of hyperfunctioning parathyroid tissue form in the neck and mediastinum, typically after neck surgery).

Due to scarring, repeat neck surgery is associated with higher complication rates; therefore, preoperative localising studies assume greater importance [52]. It is strongly recommended that redo surgery is performed by a high-volume parathyroid surgeon [3].

11 | Non-Surgical Treatments Available

11.1 | Observation

- Patients with asymptomatic PHPT and no end-organ complications require observation only. However, as a careful history typically reveals potential symptoms of PHPT (e.g., 'brain fog'), most patients are likely to be referred for surgery.
- Serum calcium, PTH and vitamin D every 3–12 months, depending on the level of hypercalcaemia.
- DXA every 1–2 years (up to every 5 years if normal) with thoracolumbar x-ray, vertebral fracture assessment or trabecular bone score if clinically indicated.
- At least annual estimated glomerular filtration rate (eGFR) and 24-h urine calcium excretion (or spot urine calcium if 24-h measurement impractical) testing; consider renal imaging for calculi and nephrocalcinosis every 5 years [2].
- Monitoring of symptoms at least annually.

Long-term follow-up is generally conducted by an endocrinologist, although it may be performed in primary care with clear instructions regarding monitoring and indications for re-referral to a specialist. Over time, a proportion of patients with PHPT under observation will develop an indication for surgery [24].

11.2 | Medical Therapy

In patients who meet the criteria for surgical management, but are judged not fit for or decline surgery, medical therapy with cinacalcet or antiresorptives can be initiated [2]. Medical therapy may also be advised for lithium-associated PHPT due to the common occurrence of multiple gland involvement and high recurrence rates after surgery [53]. Lifestyle recommendations include maintaining a normal vitamin D concentration (aiming at >75 nmol/L generally recommended), adequate dietary calcium intake (1000–1200 mg daily) and hydration [42].

Cinacalcet is a calcimimetic agent that acts as an allosteric modulator of the CaSR, thereby reducing serum calcium and PTH concentrations. An effect on bone density has not been shown and the impact on renal complications is unclear. In contrast, antiresorptive therapy with alendronate or denosumab has shown positive impact on bone density but without a consistent calcium-lowering effect [19]. There are limited published data with zoledronic acid, but a similar profile is likely. Combination therapy is a safe option [54].

11.3 | Parathyroid Ablation

Parathyroid ablation, via microwave, radiofrequency or alcohol, offers a novel less invasive approach to the management of PHPT. This technique has been successfully employed for benign thyroid nodules and shows promising results in PHPT in limited published case series [55–57]. It is not currently recommended due to limited long-term data and a relatively higher complication rate than surgery [58].

12 | Normocalcaemic PHPT

Since its description in 2008, normocalcaemic PHPT (NHPT) has presented a challenge for clinicians. It has been defined as normal serum albumin-adjusted and ionised calcium concentrations with an elevated PTH, without an identifiable secondary cause of hyperparathyroidism such as vitamin D deficiency, inadequate dietary calcium intake, calcium malabsorption, hypercalciuria (e.g., loop diuretics), renal impairment (eGFR <60 mL/min) or medications such as antiresorptives [20]. Due to natural variability of serum calcium, measurements should be repeated over a 3–6-month period [59]. Epidemiological studies are complicated by selection bias, the use of varying definitions of NHPT and lack of adequate exclusion of all secondary hyperparathyroidism aetiologies [59]. Whether NPHPT is a real disease is unclear. It may represent an early manifestation of PHPT, as observational data suggest a small proportion of patients progress to hypercalcaemia [60]. However, it also may reflect genetic polymorphisms in the CaSR, unrecognised secondary hyperparathyroidism, use of antiresorptive medications or simply increasing age. The presence of bone and renal complications despite normocalcaemia has been inconsistently reported, and it is unclear whether they are more frequent then in the general population [59]. Until clearer epidemiological and outcomes evidence emerges, we do not recommend checking serum PTH in the absence of abnormal serum calcium. When identified, NHPT should be monitored for progression and not typically be referred for surgical management (Figure 3).

13 | Management of PHPT in Pregnancy

PHPT is uncommonly diagnosed in pregnancy, but it is important not to miss due to complication risks in both the mother (hyperemesis, nephrolithiasis, pancreatitis, fragility fracture, pre-eclampsia, eclampsia) and fetus (intrauterine growth restriction, polyhydramnios, premature delivery, stillbirth, neonatal tetany) [61]. Symptoms of PHPT may overlap with common pregnancy symptoms, such as nausea [62]. Differentiating PHPT from FHH can be challenging due to physiological changes in renal calcium handling during pregnancy. Locating pre-conception calcium concentrations and assessing serum calcium in first-degree relatives is advised;

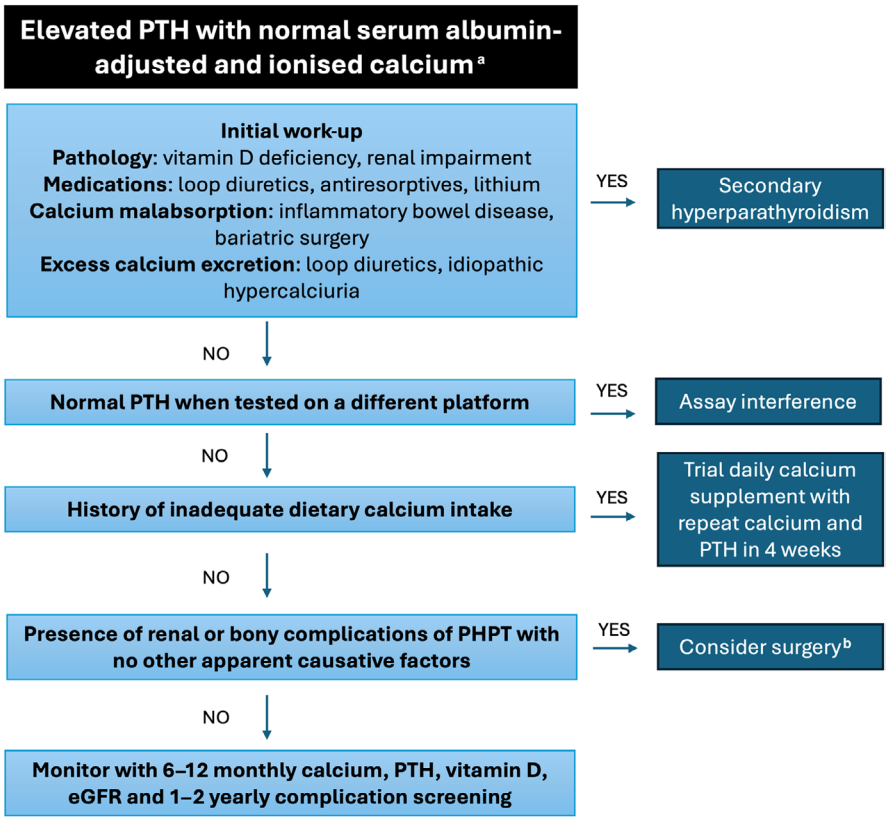

FIGURE 3 | A suggested approach to diagnosis and management of normocalcaemic primary hyperparathyroidism. eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone. [a]Outside of chronic kidney disease, measuring a serum PTH concentration is recommended only in the context of an abnormal serum albumin-adjusted or ionised calcium and should not be routinely checked. [b]Based on current lack of evidence for benefit, this situation should be rare.

genetic testing may be considered after assessment of turnaround time relative to gestation [5]. Ionised calcium is preferred for monitoring due to pregnancy-associated changes in albumin. Although mild PHPT (e.g., ionised calcium <0.12 mmol/L above the upper limit of normal [63]) in pregnancy may be kept under close surveillance, the risk of complications favours operative management [64, 65]. When possible, surgery is recommended during the second trimester, in a specialist centre with expertise in endocrinology, obstetrics, parathyroid surgery and neonatology. Neck ultrasound is preferred due to lack of radiation, although the fetal and breast radiation exposure of other modalities may be considered to guide minimally invasive surgery after a thorough risk–benefit discussion [5]. Antiresorptive therapy is not recommended during pregnancy. Cinacalcet could be considered based on low quality evidence for lack of harm in pregnancy [61]. Calcitonin does not cross the placenta but tachyphylaxis limits long-term use for hypercalcaemia. Offspring born to mothers with active PHPT require close monitoring for hypocalcaemia.

TABLE 2 | Recommendations for future research, clinical and policy priorities.

- Epidemiological studies in the Australian population, including in Aboriginal and Torres Strait Islander groups.
- Deeper understanding of non-classical primary hyperparathyroidism manifestations (e.g., cardiovascular disease) and trajectory after surgical management.
- Optimised localising imaging algorithm, particularly for multiglandular disease (i.e., Would [^{18}F]FCH PET/CT upfront be more accurate and cost-effective?).
- Development of parathyroid centres of excellence, with high volume surgeons and streamlined pathways for diagnostic work-up and perioperative care.
- High-quality epidemiological studies of the natural history and randomised controlled trials of management approaches of normocalcaemic primary hyperparathyroidism.

Abbreviations: [^{18}F]FCH, [^{18}F]fluorocholine; CT, computed tomography; PET, positron emission tomography.

14 | Conclusion

The shift of symptomatic to asymptomatic PHPT has brought challenges to appropriate patient management. The Australian and New Zealand position statement [2, 3] provides a useful framework to guide clinical decision-making, although these guidelines require further high-quality evidence to support the recommendations in several areas such as the management of non-classical manifestations of PHPT and NHPT and the ideal algorithm for localising imaging before surgery (Table 2).

Author Contributions

Elizabeth Wootton: conceptualisation, investigation, writing (original draft), writing (review and editing). **Sunita M. C. De Sousa:** writing (review and editing). **Richard L. Prince:** writing (review and editing). **Donald S. A. McLeod:** writing (review and editing). **David A. Pattison:** writing (review and editing). **Mathis Grossmann:** conceptualisation, supervision, writing (review and editing).

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** mja270194-sup-0001-supinfo.pdf.