HYPERPARATHYROIDISM

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Original Hyperparathyroidism

Clinical Guidance- Issued April 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

25OHD	25-Hydroxycholecalciferol
AWMF	Association of the Scientific Medical Societies in Germany
BMD	Bone Mineral Density
CADTH	Canadian Agency for Drugs and Technologies in Health
CAEK	German Association of Endocrine Surgeons
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
CT	Computed Tomography
CT-KUB	Computed Tomography of Kidneys, Ureters and Bladder
DXA	Dual-energy X-ray Absorptiometry
FHH	Familial Hypercalcemic Hypocalciuria
GCC	Gulf Cooperation Council
GFR	Glomerular Filtration Rate
HAS	Haute Autorite de Sante
HPT	Hyperparathyroidism
HTA	Health Technology Assessment
IDF	CHI Drug Formulary
IOPTH	Intraoperative PTH
IQWIG	Institute for Quality and Efficiency in Health Care
MEN1	Multiple Endocrine Neoplasia Type 1
MEN2A	Multiple Endocrine Neoplasia Type 2a
NCHPT	Normocalcaemic Hyperparathyroidism
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
PBAC	Pharmaceutical Benefits Advisory Committee
pHPT	Primary Hyperparathyroidism
PTH	Parathyroid Hormone
PTX	Parathyroidectomy
rHPT	Renal Hyperparathyroidism
SFDA	Saudi Food and Drug Authorization
sHPT	Secondary Hyperparathyroidism
tHPT	Tertiary Hyperparathyroidism
VFA	Vertebral Fracture Assessment

Executive Summary

Hyperparathyroidism (HPT) is a condition where the parathyroid glands become overly active, leading to abnormally high levels of parathyroid hormone (PTH) in the blood. It is categorized into primary HPT (pHPT), secondary HPT (sHPT), or tertiary HPT (tHPT) based on the underlying cause[1].

A study which is the largest of its kind among the Gulf Cooperation Council (GCC) countries, was conducted to determine the demographics and clinical characteristics of primary hyperparathyroidism (PHPT) in Saudi Arabia. The incidence of primary hyperparathyroidism (PHPT) cases has shown a rise over time compared to previous local studies, reaching 12.8 cases per 100,000 hospital population. Females outnumbered males with a ratio of 3:1, and most patients (86%) were treated as out-patients. The average age of patients was 59.8 ± 15.5 years[2].

Primary hyperparathyroidism is characterized by the abnormal release of parathyroid hormone (PTH), leading to high levels of calcium in the blood (hypercalcemia). While the condition typically arises spontaneously, familial forms of primary hyperparathyroidism are also well-identified. Around 75 to 80 percent of primary hyperparathyroidism cases are asymptomatic, meaning patients do not exhibit any signs or symptoms of hypercalcemia. However, there are certain signs and symptoms that may be present in these patients, which are not clearly linked to primary hyperparathyroidism. These include hypertension, left ventricular hypertrophy, valvular or myocardial calcification, peptic ulcer disease, pancreatitis, gout or pseudogout, normocytic normochromic anemia, weakness, easy fatigability, lassitude, anxiety, cognitive difficulties, somatic complaints, and clinical depression[3].

Parathyroidectomy is the definitive treatment for primary hyperparathyroidism. Patients who are asymptomatic and fulfill the criteria recommended by the National Institutes of Health (NIH) guidelines may be eligible for medical observation instead of opting for surgical treatment with parathyroidectomy. Recommendations include modest intake of calcium (1,000 to 1,200 mg per day) and vitamin D (400 to 600 IU per day). At present, there are no medical treatments that can fully cure primary hyperparathyroidism. However, in postmenopausal women, estrogen has shown potential in reducing PTH-stimulated bone resorption. Ongoing research is investigating the effects of newer oral bisphosphonates, calcimimetics, and raloxifene in the management of the condition[3].

Secondary hyperparathyroidism occurs when the parathyroid glands respond either physiologically or pathophysiologically to low levels of calcium to maintain calcium balance within the body. This condition can arise due to vitamin D deficiency or inadequate intake of calcium. Most of the symptoms of secondary hyperparathyroidism are due to the underlying cause. People with vitamin D deficiency may notice muscle aching and weakness, or aching bones. In severe

cases, they can develop osteomalacia (soft bones) which can cause fractures and bone deformity. Secondary hyperparathyroidism is treated medically by restoring vitamin D and calcium levels if deficient or preventing excess phosphate levels in patients with chronic kidney disease, rather than needing surgical treatment[3].

CHI issued Hyperparathyroidism clinical guidance after thorough review of renowned international and national clinical guidelines in April 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Hyperparathyroidism clinical guidance and seeks to offer guidance for the effective management of hyperparathyroidism. It provides an **update on the Hyperparathyroidism Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely Evaluation and Management of Primary Hyperparathyroidism: **Summary Statement and Guidelines from the Fifth International Workshop 2022.** Moreover, new guidelines are added to the report such as 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 (2021)** and **Management of primary and renal hyperparathyroidism: guidelines from the German Association of Endocrine Surgeons (CAEK) (2021).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug **Etelcalcetide** (**Parsabiv**®) in the CHI formulary for hyperparathyroidism while delisting **calcitriol** since it is no longer SFDA registered.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Hyperparathyroidism therapeutic management.

Below is a table summarizing the major changes based on the different hyperparathyroidism guidelines used to issue this report.

Table 1. General Recommendations for the Management of Hyperparathyroidism

Management of Hyperparathyroidism		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Patients diagnosed with symptomatic primary hyperparathyroidism (PHPT) and who are considered suitable candidates for surgery based on an evaluation of surgical risks and life expectancy should be recommended for surgical treatment.	Not graded	The endocrine society of Australia, the Australian & New Zealand endocrine surgeons, and the Australian & New Zealand bone and mineral society[4]
The recommended calcium intake aligns with the Institute of Medicine guidelines: 800 mg/day for females under 50 and males under 70; 1000 mg/day for females over 50 and males over 70.	Not graded	Summary Statement and Guidelines from the Fifth International Workshop[5]
In patients with PHPT and vitamin D insufficiency (25OH vitamin D < 30 ng/mL (75 nmol/L) or deficiency (< 12 ng/mL; < 30 nmol/L), we suggest vitamin D supplementation.	Weak recommendation based on very low-quality evidence	Summary Statement and Guidelines from the Fifth International Workshop[5]
For individuals diagnosed with primary hyperparathyroidism (PHPT) and serum calcium levels surpassing 11.0 mg/dL (0.25 mmol/L) above the upper normal limit, who opt not to undergo parathyroidectomy (PTX), we recommend considering cinacalcet.	Weak recommendation based on low quality of evidence	Summary Statement and Guidelines from the Fifth International Workshop[5]
In patients with low BMD who do not undergo PTX, we suggest bisphosphonates (eg, alendronate) or denosumab.	Weak recommendation based on very low-quality evidence	Summary Statement and Guidelines from the Fifth International Workshop[5]

Women in their reproductive years who are diagnosed with primary hyperparathyroidism (PHPT) are advised to consider curative surgery. before becoming pregnant, whenever possible.	Not graded	The endocrine society of Australia, the Australian & New Zealand endocrine surgeons, and the Australian & New Zealand bone and mineral society[4]

At the end of the report, "a key recommendation synthesis section is added highlighting the latest updates in Insomnia clinical and therapeutic management" and "Appendices are available for further information".

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Hyperparathyroidism report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the April 2020 CHI Hyperparathyroidism Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 **Nice guidelines of Hyperparathyroidism (primary):** diagnosis, assessment, and initial management **[2019]**	N/A*
1.2 Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: **Summary Statement from the Fourth International Workshop [2014]**	1.1.1 Evaluation and Management of Primary Hyperparathyroidism: **Summary Statement and Guidelines from the Fifth International Workshop 2022**

1.3 **The American Association of Endocrine Surgeons Guidelines** for Definitive Management of Primary Hyperparathyroidism **[2016]**	N/A*
1.4 **European Society of Nephrology guidelines** for Secondary Hyperparathyroidism: Pathogenesis, Disease Progression, and Therapeutic Options **[2011]**	N/A*
1.5 **[2018] Endocrine Society guidelines** of Primary Hyperparathyroidism	N/A*

*****: *No updated versions available*

1.1.1 Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop (2022)

*Please refer to **Section 1.2** of CHI Hyperparathyroidism original clinical guidance*

Summary Statement and Guidelines from the Fifth International Workshop 2022 for the evaluation and Management of Primary Hyperparathyroidism[5] introduced a set of recommendations accompanied by a grading scheme as well as quality of evidence, outlined as follows:

Table 3. Strength of Recommendations

Grading Scheme for Recommendations	
Weak	There is likely to be an important variation in the decision that informed persons are likely to make
Strong	All or almost all persons would choose that intervention

Table 4. Quality of Evidence

Quality of evidence	
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect

High	The authors have a lot of confidence that the true effect is similar to the estimated effect

Diagnosis

- Hypercalcemic primary hyperparathyroidism (PHPT) is characterized by an increased level of serum calcium, which is corrected for albumin levels, along with a higher or inappropriately normal level of intact parathyroid hormone (PTH) measured using a second or third-generation assay, observed on at least two separate occasions, with a minimum interval of 2 weeks between each measurement.
- Familial hypocalciuric hypercalcemia (FHH) might be considered in younger individuals exhibiting a urinary calcium/creatinine clearance ratio of less than 0.01, or those who have a family history of hypercalcemia.
- Lithium and thiazides are both medications that can lead to hypercalcemia and elevated PTH levels above the normal range.
- The occurrence of ectopic secretion of PTH causing hypercalcemia in association with malignant tumors is extremely rare.
- Normocalcemic primary hyperparathyroidism (PHPT) is characterized by having normal adjusted total calcium and ionized calcium levels, while showing elevated intact PTH levels (measured using a second or third generation assay) on at least two occasions spanning 3 to 6 months. This diagnosis is made after ruling out all other potential causes for secondary hyperparathyroidism.

Clinical Phenotypes of PHPT

- Symptomatic PHPT: associated with overt skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis.
- Asymptomatic PHPT: no overt symptoms or signs; typically discovered by biochemical screening. Two forms of asymptomatic PHPT are defined after evaluation:
    - with target organ involvement
    - without target organ involvement
- Normocalcemic PHPT: Skeletal or renal complications may or may not exist in those whose presentation fits this definition.

Patients Evaluation

- Biochemical: Measure adjusted total serum calcium (ionized if normocalcemic PHPT is a consideration), phosphorus, intact PTH, 25OHD, creatinine.
- Skeletal: Three-site dual-energy X-ray absorptiometry (DXA) (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (vertebral fracture assessment [VFA] or vertebral X-rays); trabecular bone score (TBS) if available
- Renal: Estimated glomerular filtration rate (eGFR) or, preferably, creatinine clearance, 24-hour urinary calcium and for biochemical risk factors for stones; imaging for nephrolithiasis/nephrocalcinosis
- Nonclassical manifestations (neurocognitive, quality of life, cardiovascular): there is no data to support routine evaluation for these putative manifestations.
- Genetic: genetic evaluation should be considered for patients less than 30 years old, those with multigland disease by history or imaging, and/or those with a family history of hypercalcemia and/or a syndromic disease
- In patients with asymptomatic PHPT, we recommend surgery to cure the disease (strong recommendation/high quality evidence).

Parathyroidectomy

- Although parathyroidectomy is an option for all patients, with concurrence of the patient and the physician and if there are no contraindications, the panel recommends surgery in all those in whom one or more of the following is present (including those who are asymptomatic):
    - Serum calcium >1 mg/dL (0.25 mmol/L) above the upper limit of normal or
    - Skeletal involvement:
        a. A fracture by VFA or vertebral X-ray or
        b. Bone mineral density (BMD) by T-score ≤ 2.5 at any site or
    - Renal involvement:
        a. eGFR or creatinine clearance < 60 mL/min
        b. Nephrocalcinosis or nephrolithiasis by X-ray, ultrasound, or other imaging modality
        c. Hypercalciuria (eg, >250 mg/day in women; >300 mg/day in men) or
    - Age < 50 years (no other indications are necessary; age < 50 years is a sufficient indication)

- Surgery should be performed by an experienced parathyroid surgeon.
- Surgery cannot be recommended to improve neurocognitive function, quality of life, and/or cardiovascular indices because the evidence is inconclusive.

Medical Management of PHPT

Patients with PHPT who do not meet guidelines for parathyroidectomy can be followed without pharmacological intervention. For those who choose not to have surgery, but who meet specific guidelines (e.g., calcium or bone mineral density), medical options are available as recommended by the Panel.

- The calcimimetic cinacalcet would be expected to reduce the serum calcium without necessarily improving bone mineral density (BMD).
- In patients with PHPT and serum calcium levels >11.0 mg/dL (>0.25 mmol/L) above the upper limit of normal who do not undergo PTX, we suggest cinacalcet (weak recommendation based on low quality of evidence).
- Vitamin D supplementation: the panel recommends levels of 25OHD >30 ng/mL and < the upper limit of normal for the laboratory reference range (eg, < 50 ng/mL)
- In patients with PHPT and vitamin D insufficiency (25OH vitamin D < 30 ng/mL (75 nmol/L) or deficiency (<12 ng/mL; <30 nmol/L) we suggest vitamin D supplementation (weak recommendation based on very low-quality evidence)
- Calcium intake/supplementation should follow the Institute of Medicine nutritional guidelines: 800 mg/day for women < 50 and men < 70 years old; and 1000 mg/day for women > 50 and men > 70 years old.
- In patients with low BMD who do not undergo PTX, we suggest bisphosphonates (eg, alendronate) or denosumab (weak recommendation based on very low-quality evidence)
- Bisphosphonates, primarily alendronate, have been shown to improve BMD and to reduce bone turnover in PHPT, but without any consistent reductions in the serum calcium concentration.
- Estrogen has been shown to increase BMD. Its effect on the reduction of serum calcium is inconsistent.
- Raloxifene cannot be recommended because the data is insufficient to reach any conclusions.

Monitoring requirements in patients who do not undergo Parathyroidectomy (PTX)

- Serum calcium and 25OHD concentrations: annually. PTH levels can also be measured, as clinically indicated.

Skeletal:

- Three-site DXA every 1 or 2 years unless the BMD is normal.
- Vertebral X-ray, VFA, or TBS if clinically indicated.

Renal:

- Creatinine clearance (preferred over eGFR), annually.
- Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated.
- 24-Hour urine for calcium, if clinically indicated.

Pregnancy considerations

- Mild cases should be managed by maintaining good hydration and monitoring calcium levels.
- Bisphosphonates and denosumab should not be used.
- Data is very limited on use of cinacalcet.
- Consider surgery in the second trimester for patients with serum calcium >11.0 mg/dL and for whom surgery is not contraindicated.
- Preoperative imaging should be limited to ultrasound.
- If surgery is deferred, the neonate should be closely monitored for hypocalcemia.
- If surgery is deferred, PTX should be done after delivery, and before a subsequent pregnancy.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Hyperparathyroidism report, along with their recommendations.

Table 5. List of Additional Guidelines

Additional Guidelines
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 (2021)**
Management of primary and renal hyperparathyroidism: guidelines from the German Association of Endocrine Surgeons (CAEK) (2021)

1.2.1 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 (2021)

The main points of 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 (2021)[4] are detailed below:

PHPT can be classified according to the following types:

- **Classical PHPT:** Classical PHPT is characterized by high serum calcium and elevated serum PTH due to parathyroid neoplasia. Surgical removal of the affected tissue corrects hypercalcemia and improves symptoms. Up to 25% of PHPT cases may have elevated calcium with normal PTH levels.
- **Normocalcaemic HPT (NCHPT):** Normocalcemic hyperparathyroidism (NCHPT) is characterized by consistently high levels of serum PTH and both adjusted and ionized calcium within the reference range. The patient should have normal kidney function and no other secondary causes of hyperparathyroidism, such as vitamin D deficiency, kidney problems, idiopathic hypercalciuria, malabsorption, Paget's disease, or iatrogenic causes like thiazides, lithium, denosumab, and bisphosphonates. Limited and inconsistent data are available regarding the natural history of NCHPT, but some patients with NCHPT may eventually progress into classical hyperparathyroidism over time.

- Serum calcium should be measured in patients with reduced bone mineral density, minimal trauma fractures, renal stones, in patients taking lithium, in patients with fatigue, musculoskeletal or neuropsychiatric complaints or altered mental status.
- Serum calcium, PTH, and 25-hydroxy vitamin D should be measured in patients >40 years before undergoing thyroid surgery.

Diagnostic investigations and criteria

- In patients with normal kidney function and albumin levels, measure serum calcium adjusted for albumin levels. If renal function or albumin levels are not normal, use ionized calcium to assess serum calcium levels.
- If a patient shows elevated calcium levels adjusted for albumin, it is advisable to repeat the test or request ionized calcium along with serum phosphate, renal function, parathyroid hormone (PTH), and 25-hydroxy vitamin D levels for further evaluation.
- For patients with confirmed hypercalcemia, assess the urinary calcium: creatinine clearance ratio using either a 24-hour urinary calcium collection or a second morning void urinary calcium sample. This differentiation is crucial to distinguish between hyperparathyroidism and familial hypercalcemic hypocalciuria (FHH).
- Individuals diagnosed with primary hyperparathyroidism are advised to undergo a DXA (Dual-energy X-ray absorptiometry) scan of the hip, lumbar spine, and distal radius.
- All patients with primary hyperparathyroidism (PHPT) should undergo thoracolumbar imaging initially. Parathyroidectomy should be taken into consideration for patients with vertebral compression fractures, whether they are symptomatic or asymptomatic.
- For patients with primary hyperparathyroidism (PHPT) who do not have other indications for parathyroidectomy, it is recommended to consider renal tract imaging. Possible imaging modalities include renal tract ultrasound and X-ray KUB (Kidneys, Ureters, and Bladder). A non-contrast CT scan (CT-KUB) is also a viable option, which exposes the patient to relatively low radiation and provides excellent sensitivity in detecting potential issues.
- Even if there is no prior history of urinary tract calculi or any findings on imaging, it is still recommended to evaluate urinary calcium excretion. For patients with confirmed hyperparathyroidism and hypercalciuria, the possibility of undergoing parathyroidectomy should be considered.

Surgery

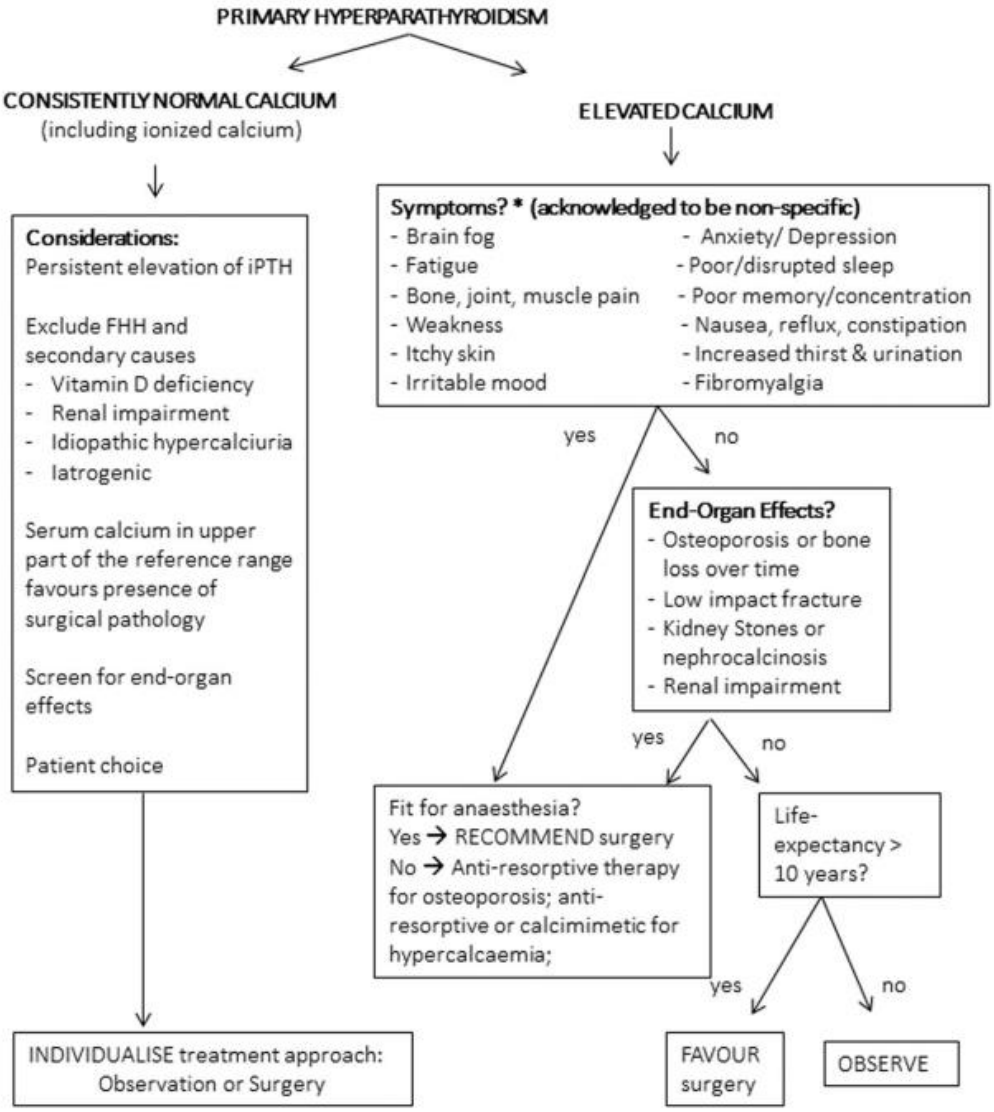

Figure 1. *Management Algorithm for Adults with Primary Hyperparathyroidism. Retrieved from Milat F, Ramchand SK, Herath M, et al. Primary hyperparathyroidism in adults - (Part I) assessment and medical management: Position statement of the endocrine society of Australia, the Australian & New Zealand endocrine surgeons, and the Australian & New Zealand bone and mineral society. Clin Endocrinol (Oxf). Published online 2021. doi:10.1111/cen.14659.*

- Patients diagnosed with symptomatic primary hyperparathyroidism (PHPT) and who are considered suitable candidates for surgery based on an evaluation of surgical risks and life expectancy should be recommended for surgical treatment.

- In patients with primary hyperparathyroidism (PHPT) who have an elevated risk of fractures, parathyroidectomy is recommended, considering their current bone density and fracture history.
- Patients diagnosed with primary hyperparathyroidism (PHPT) and showing signs of renal tract calcification, such as nephrolithiasis (kidney stones) and nephrocalcinosis, should undergo parathyroidectomy.
- For patients experiencing musculoskeletal symptoms associated with primary hyperparathyroidism (PHPT), parathyroidectomy should be taken into consideration as a possible treatment option.
- For patients with neurocognitive and/or neuropsychiatric symptoms related to primary hyperparathyroidism (PHPT), it is advisable to consider parathyroidectomy as a recommended course of action.
- Patients with slightly elevated calcium levels should undergo assessment and management similar to those with more severe hypercalcemia.

Management of asymptomatic hyperparathyroidism

Table 6. 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)

Retrieved from Milat F, Ramchand SK, Herath M, et al. 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. Clin Endocrinol (Oxf). Published online 2021. doi:10.1111/cen.14659.

- Before deciding on observation rather than surgery, asymptomatic patients with primary hyperparathyroidism (PHPT) should be evaluated for any signs of

end-organ complications, such as decreased bone mineral density, vertebral compression fractures, or kidney stones. The presence of these complications would be an indication of surgery in patients with a reasonable life expectancy.

- Patients diagnosed with asymptomatic primary hyperparathyroidism (PHPT) and no signs of end-organ damage, who are medically capable of tolerating anesthesia, and have a life expectancy of more than 10 years, should be provided with information regarding the advantages and disadvantages of surgical intervention compared to observation.
- Patients who are monitored or managed medically should undergo annual evaluation.

Table 7. 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

Retrieved from Milat F, Ramchand SK, Herath M, et al. 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. Clin Endocrinol (Oxf). Published online 2021. doi:10.1111/cen.14659.

Management of hyperparathyroidism in pregnancy

- For women of childbearing age diagnosed with primary hyperparathyroidism (PHPT), curative surgery is recommended before pregnancy, whenever feasible.
- If a pregnant woman is diagnosed with severe primary hyperparathyroidism (PHPT), it is advised to undergo parathyroidectomy during the second

trimester of pregnancy. Ultrasound is the preferred method for localizing the affected parathyroid gland.

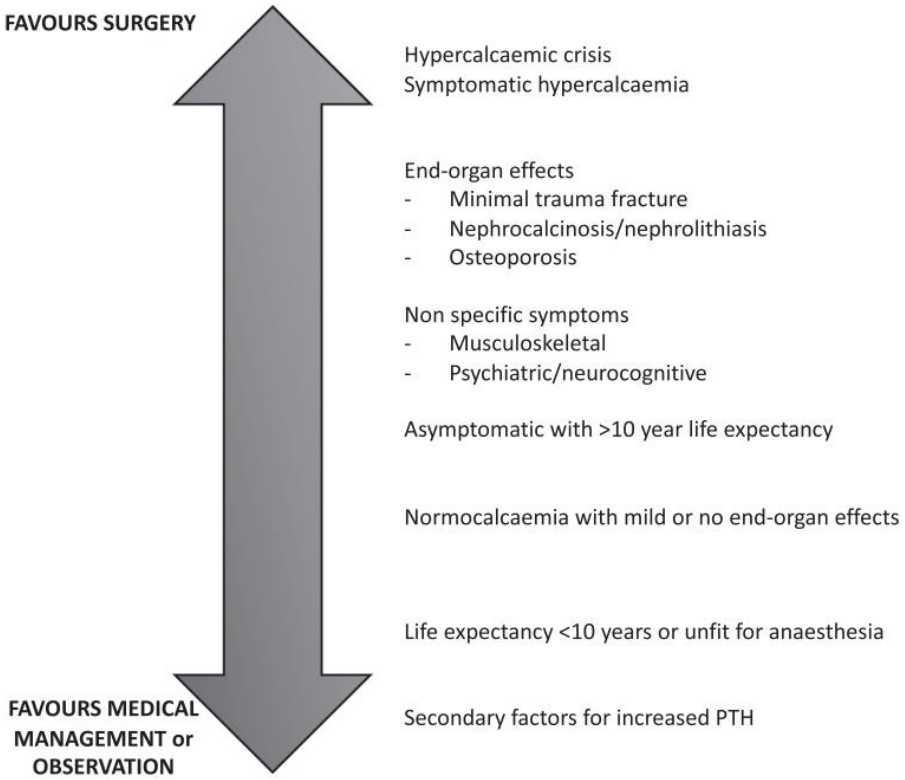

Figure 2. *Recommendations Favoring Medical Management/Observation Versus Surgery for Different Symptomatology. Retrieved from Milat F, Ramchand SK, Herath M, et al. Primary hyperparathyroidism in adults - (Part I) assessment and medical management: Position statement of the endocrine society of Australia, the Australian & New Zealand endocrine surgeons, and the Australian & New Zealand bone and mineral society. Clin Endocrinol (Oxf). Published online 2021. doi:10.1111/cen.14659.*

- In a patient with PHPT, a palpable neck mass, severely elevated calcium or PTH, and large tumor size are features suspicious for parathyroid carcinoma and should prompt careful evaluation.
- Patients with primary hyperparathyroidism (PHPT) who have early onset or involvement of multiple glands, parathyroid carcinoma, a family history of PHPT or related tumors, and/or a personal history of other features associated with PHPT predisposition syndromes are recommended to undergo genetic testing. Additionally, genetic testing should be considered for hypercalcemic patients who exhibit features indicative of familial hypocalciuric hypercalcemia (FHH).
- The choice of genes to be examined in genetic testing should be based on the specific indication for testing. In cases where a predisposition syndrome for

primary hyperparathyroidism (PHPT) is suspected, the following genes should be assessed: MEN1, CDC73, RET, CDKN1B, GCM2, and CASR. On the other hand, suspected familial hypocalciuric hypercalcemia (FHH) should involve the assessment of CASR, AP2S1, and GNA11 genes.

1.2.2 Management of Primary and Renal Hyperparathyroidism: Guidelines from the German Association of Endocrine Surgeons (CAEK) (2021)

The German Association of Endocrine Surgeons (CAEK) (2021) on the management of primary and renal hyperparathyroidism[6] introduced the following methods for grading:

"All of the participants discussed and voted on the remaining controversial items. Consensus level was graded as high consensus (> 95% approval, +++) or consensus (75–94% approval, ++) in accordance with the AWMF regulations. Finally, all recommendations were passed with high consensus or consensus."

A. Primary hyperparathyroidism

Epidemiology and diagnosis of pHPT

- The biochemical assessment for diagnosing primary hyperparathyroidism (pHPT) should involve multiple measurements of serum calcium, parathyroid hormone (PTH), creatinine, and 25-hydroxyvitamin D levels (consensus ++).
- To rule out familial hypocalciuric hypercalcemia (FHH), it is recommended to conduct a 24-hour urine calcium measurement (consensus ++).

Symptoms of pHPT

- The biochemical diagnosis of primary hyperparathyroidism (pHPT) should be complemented by an assessment of personal and family medical history, which should encompass both typical and associated symptoms of pHPT (consensus ++).
- It is possible to conduct dual-energy X-ray absorptiometry (DXA) preoperatively, which can assess various skeletal areas such as the lumbar spine, femoral head, or distal radius (high consensus +++).

Indications and outcomes of surgery for pHPT

- Surgery is the sole curative treatment for primary hyperparathyroidism (pHPT). Parathyroidectomy is recommended regardless of the patient's age. In specific cases where individuals are asymptomatic with mildly elevated serum calcium levels, surveillance of pHPT can be considered (consensus ++).

- Parathyroidectomy during pregnancy can be safely performed in the second trimester (consensus ++).
- Parathyroidectomy is strongly indicated for patients with nephrolithiasis or nephrocalcinosis (high consensus +++)
- Parathyroidectomy is recommended for individuals with osteoporosis and fragility fractures, particularly those affecting the spine or occurring after minor trauma (consensus ++).
- Parathyroidectomy is recommended for patients with typical psychiatric and neurocognitive symptoms (consensus ++)

Preoperative management of pHPT

- Individuals with 25(OH) vitamin D levels below 20 ng/mL are advised to initiate vitamin D supplementation. It is also recommended to conduct short-term serum calcium testing in these patients (high consensus +++).

Hypercalcemic crisis

- Patients experiencing a hypercalcemic crisis should receive in-hospital care, which includes fluid resuscitation, followed by parathyroidectomy.
- Both pre-operative and post-operative laryngoscopy should be conducted for every patient undergoing surgery for primary hyperparathyroidism (pHPT) or recurrent hyperparathyroidism (rHPT).

Operative therapy for pHPT Perioperative management

1. **Perioperative management**

- After undergoing parathyroidectomy, there is generally no need for postoperative thromboembolic prophylaxis. However, exceptions to this are protracted and oncologic cervical procedures or situations where patients have elevated individual risk factors. (high consensus +++)
- The routine use of antimicrobial prophylaxis is not generally recommended for parathyroid surgery. The decision to administer antimicrobial prophylaxis should be based on individual and intraoperative risk factors. (high consensus +++).

2. **Intraoperative PTH monitoring**

- IOPTH (Intraoperative parathyroid hormone) should be employed for focused parathyroid surgery and can also be utilized for bilateral neck exploration to rule out multiglandular disease (consensus ++).
- To ensure consistency and accuracy, it is highly recommended to implement a standardized protocol for IOPTH with clearly defined interpretation criteria (high consensus +++).

- The interpretation of IOPTH results should take into account intraoperative PTH peaks, delayed declines potentially caused by impaired renal function, as well as very high or low initial values (high consensus +++).
- In specific, highly selective cases where there is concordant localization of a single-gland adenoma, surgeons have the discretion to decide not to use IOPTH (high consensus +++).
- For defining the side of the hyperfunctional parathyroid gland, intraoperative bilateral venous sampling can be highly useful (high consensus +++).

3. Postoperative management

- After parathyroid surgery, patients should undergo postoperative monitoring for cervical hematoma following the guidelines typically used for thyroid surgery. In cases where secondary hemorrhage is suspected, immediate airway management and decompression are necessary.
- It is highly recommended to assess postoperative parathyroid function on the first postoperative day. This assessment should include measuring calcium and PTH levels to check for hypoparathyroidism (high consensus +++).
- Following a successful parathyroidectomy, around 50% of patients may experience early hypocalcemia. In approximately 10% of cases, this condition is attributed to "hungry bone syndrome." In light of this, it may be advisable to consider prophylactic supplementation with oral calcium and vitamin D (consensus ++).
- In the event of postoperative hypoparathyroidism, it should be managed through the administration of oral calcium and active vitamin D. Furthermore, it is important to conduct follow-up laboratory tests to monitor and manage the condition effectively (consensus ++).

Reoperations for persistent or recurrent pHPT

- Reoperations for primary hyperparathyroidism (pHPT) should only be considered in patients who have positive preoperative localization studies, and these reoperations should be conducted with the use of intraoperative PTH monitoring (consensus +++).
- Patients undergoing reoperative parathyroidectomy should undergo the same postoperative monitoring for cervical hemorrhage, recurrent laryngeal nerve paresis, and hypocalcemia as patients undergoing primary operations (high consensus +++).
- For patients who have undergone parathyroid surgery, it is important to obtain biochemical follow-up for a minimum of 6 months. The duration of follow-up may need to be extended if hypercalcemia, hypocalcemia, or a

family history of hereditary hyperparathyroidism (HPT) is identified (high consensus +++).

B. Renal hyperparathyroidism (rHPT)

I. Indication for parathyroidectomy in rHPT

- In patients with recurrent hyperparathyroidism (rHPT), parathyroidectomy is recommended when all conservative treatment options have been exhausted, and clinical symptoms are present (consensus ++).

II. Indication for parathyroidectomy before and after renal transplantation

- For symptomatic patients with recurrent hyperparathyroidism (rHPT) who are candidates for renal transplantation, subtotal parathyroidectomy may be considered as part of the treatment plan (high consensus +++).
- In cases of severe symptomatic hypercalcemia occurring within the first few months after renal transplantation, a multidisciplinary medical team should be involved in the management. Early consideration of subtotal parathyroidectomy may be indicated as part of the treatment approach (consensus ++).

Preoperative localization procedures in rHPT

- For patients diagnosed with recurrent hyperparathyroidism (rHPT), it is highly recommended to undergo preoperative ultrasound. This ultrasound serves the purpose of localizing hyperplastic parathyroid glands and assessing for any concurrent thyroid disease (consensus ++)
- Patients who are on dialysis face an elevated perioperative risk, and their cardiovascular comorbidities should be taken into account. In cases where patients are on dialysis, parathyroidectomy is typically recommended to be performed the day following the last dialysis session (high consensus +++).

Surgery for rHPT

- In the context of recurrent hyperparathyroidism (rHPT), IOPTH (Intraoperative parathyroid hormone) can be employed as a predictive tool for determining whether the condition has been successfully treated. However, defining specific criteria for PTH decrease in rHPT can be more challenging, as it depends on the PTH assay used. Therefore, the effective use of IOPTH relies on the experience and expertise of the surgeon (consensus ++).
- For older patients who do not have planned renal transplantation, a parathyroidectomy without autotransplantation and without thymectomy can be considered as an option. (high consensus +++)

- Regardless of the number of parathyroid glands removed during surgery, a cervical thymectomy can be carried out to reduce the risk of persistent or recurrent hyperparathyroidism (rHPT) (high consensus +++).
- For autotransplantation, the least nodular altered parathyroid tissue should be selected (high consensus +++).
- Cryopreservation of parathyroid tissue can be conducted after total parathyroidectomy or during reoperative parathyroid surgery. However, if vascularized parathyroid tissue is intentionally left in its original location, cryopreservation can be omitted (high consensus +++).
- Postoperative surveillance, as well as the adjustment and reduction of the initial calcium and vitamin D medications, is advisable, particularly when these medications are initially prescribed in substantial doses. Such postoperative management should ideally be overseen by an experienced nephrologist (consensus ++).

Complications and management in patients with rHPT

- Postoperative hemorrhage following parathyroidectomy for recurrent hyperparathyroidism (rHPT) tends to occur more frequently compared to primary hyperparathyroidism (pHPT). In the event of postoperative bleeding, it is crucial to promptly perform surgical revision, and perioperative antibiotic prophylaxis should be administered as a mandatory measure (high consensus +++).
- According to the multimorbidity of patients with rHPT, perioperative single-shot antibiotics should be applied (consensus ++)

Persistence and recurrence of rHPT

- For reoperative rHPT, preoperative localization procedures must be performed (high consensus +++).

C. Secondary hyperparathyroidism without renal insufficiency

- The treatment approach for secondary hyperparathyroidism (sHPT) typically involves high doses of vitamin D and possibly calcium supplementation, along with osteoporosis treatment. In such cases, there is generally no indication for surgery.

D. Hereditary forms of hyperparathyroidism

1. Multiple endocrine neoplasia type 1

- For patients diagnosed with primary hyperparathyroidism (pHPT) and who are younger than 30 years old, it is recommended to undergo gene mutation analysis of potential candidate genes based on their family history. This should be carried out after genetic counseling. (consensus ++).
- When a MEN1 (Multiple Endocrine Neoplasia type 1) mutation is detected, it is highly advisable to examine and monitor specific organ manifestations corresponding to MEN1. In such cases, parathyroidectomy should be performed as soon as pHPT is diagnosed (high consensus +++).
- For patients with MEN1, subtotal or total parathyroidectomy, along with thymectomy and autotransplantation, is indicated. To minimize the risk of permanent hypoparathyroidism, selective resection of enlarged parathyroids can be considered. Additionally, patients must be informed about the possibility of reoperation for recurrent pHPT (high consensus +++).

2. Multiple endocrine neoplasia type 2a

- For pHPT in MEN2A syndrome, selective parathyroidectomy with IOPTH is recommended for markedly diseased glands (high consensus +++).

E. Primary hyperparathyroidism in children and adolescents

- In individuals aged 20 years or younger who present with typical symptoms such as fatigue, weakness, lack of concentration, and nephrolithiasis, it's important to note that 95% of these patients with primary hyperparathyroidism (pHPT) exhibit these symptoms. In such cases involving children or adolescents with these symptoms, it is advisable to conduct laboratory tests to measure serum calcium and parathyroid hormone (PTH) levels (high consensus +++).
- Primary hyperparathyroidism (pHPT) in children and adolescents tends to be more frequently caused by smaller and ectopic adenomas. Consequently, preoperative imaging and surgery can be challenging procedures. It is recommended that these procedures be carried out exclusively by experienced surgeons to ensure appropriate care and management (high consensus +++).

Section 2.0 Drug Therapy in Hyperparathyroidism

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

After April 2020, there have been no hyperparathyroidism drugs that have received FDA or EMA approval. Nevertheless, *etelcalcetide and denosumab* were registered in the SFDA list. Hence, relevant information pertaining to these drugs can be found below.

2.1.1 Etelcalcetide

This section includes pertinent information regarding the use of *etelcalcetide* (Parsabiv®) in hyperparathyroidism.

Table 8. Drug Therapy with Etelcalcetide

SCIENTIFIC NAME **Etelcalcetide**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	No
PMDA	Yes
Indication (ICD-10)	E21, N25.81
Drug Class	Calcimimetic
Drug Sub-class	N/A
ATC Code	H05BX
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous
Dose (Adult) [DDD]*	Hyperparathyroidism, secondary (dialysis-dependent chronic kidney disease):

	• IV: Initial: 5 mg IV bolus 3 times per week at the end of hemodialysis. • Titrate dose in 2.5 mg or 5 mg increments not more frequently than every 4 weeks to a dose that maintains PTH levels within recommended target range and corrected serum calcium within the normal range
Maximum Daily Dose Adults*	Maximum maintenance dose: 15 mg three times per week
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	<u>Altered kidney function:</u> No dosage adjustment necessary <u>Hepatic impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling. <u>Dosing: Adjustment for Toxicity: Adult Hypocalcemia (patients with secondary hyperparathyroidism):</u> • If corrected serum calcium ≥7.5 mg/dL but <8.4 mg/dL (>1.87 mmol/L but <2.1 mmol/L): Mild (eg, serum calcium 8 to <8.4 mg/dL [2 to <2.1 mmol/L]) or asymptomatic hypocalcemia due to calcimimetic may not require treatment. In patients with more significant or symptomatic hypocalcemia, may consider decreasing or temporarily discontinuing etelcalcetide or use of calcium-containing phosphate binders, vitamin D analogs, and/or adjustment of dialysate calcium content to raise calcium

	levels while avoiding hypercalcemia. If the etelcalcetide dose is stopped, reinitiate at a lower dose when the PTH is within the target range and hypocalcemia has been corrected. • If corrected serum calcium <7.5 mg/dL (<1.87 mmol/L) or if hypocalcemia symptoms persist despite treatment: Withhold etelcalcetide (and address any other predisposing factors for hypocalcemia) until corrected serum calcium ≥8 mg/dL (≥2 mmol/L) and/or symptoms of hypocalcemia resolve. Reinitiate etelcalcetide at a dose 5 mg lower than the last administered dose. If the last administered dose was 2.5 or 5 mg, reinitiate at a dose of 2.5 mg. • PTH levels below the target range: Decrease dose or temporarily discontinue therapy. Re-initiate at a lower dose when PTH is within target range (and if corrected serum calcium is at or above the lower limit of normal).
Prescribing edits*	ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Calcimimetics are typically used when other treatment approaches, such as dietary modifications, phosphate binders, and vitamin D supplementation, have not effectively controlled parathyroid hormone (PTH) levels.	

EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Hypocalcemia, hypophosphatemia, diarrhea, nausea, muscle spasm Most serious: Adynamic bone disease, QT prolongation, ventricular arrhythmias, upper GI bleeding, severe hypocalcemia.
Drug Interactions	**Category X**: • Cinacalcet • Levoketoconazole • Pimozide • Sertindole
Special Population	N/A
Pregnancy	Adverse events were observed in animal reproduction studies at doses which also caused maternal toxicity (including hypocalcemia).
Lactation	It is not known if etelcalcetide is present in breast milk. Due to the potential for hypocalcemia in a breastfeeding infant, breastfeeding is not recommended by the manufacturer.
Contraindications	Hypersensitivity to etelcalcetide or any component of the formulation.
Monitoring Requirements	Monitor signs/symptoms of hypocalcemia (eg, muscle spasms, myalgia, paresthesia, seizure, tetany); worsening signs/symptoms of heart failure. In patients with seizure disorders, closely monitor albumin-corrected serum calcium levels. In patients at risk for GI bleeding (eg, gastritis, esophagitis, ulcers, severe vomiting), monitor for worsening of nausea and vomiting and for

	signs/symptoms of GI bleeding and ulceration. In patients at risk for QT prolongation and/or ventricular arrhythmia, closely monitor albumin-corrected serum calcium levels and QT interval. Monitor albumin-corrected serum calcium levels at baseline and 1 week after initiation or dosage adjustment; after maintenance dose is established, monitor every 4 weeks. Monitor parathyroid hormone levels at baseline and 4 weeks after initiation or dosage adjustment and periodically thereafter.
Precautions	Heart failure: Patients with heart failure may experience worsening of their heart failure with use; additional monitoring may be required. Seizure disorder: Use with caution in patients with a history of seizure disorder; seizure threshold is lowered by significant decreases in serum calcium.
Black Box Warning	N/A
REMS	N/A

Clinical trials – Etelcalcetide

The efficacy and safety of PARSABIV for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease receiving hemodialysis three times per week were evaluated in two phase 3 26-week, randomized, double-blind, placebo-controlled studies.

Baseline characteristics in both trials were balanced. The primary efficacy endpoint was the proportion of patients achieving a greater than 30% reduction from baseline mean PTH concentrations during the assessment phase (week 20 to week 27). The secondary efficacy endpoint was the proportion of patients achieving a mean PTH of 300 pg/mL or less. Patients were administered etelcalcetide or placebo three times a week following hemodialysis.

In Trial 1, 254 patients were randomized to the etelcalcetide arm, and 254 patients were given placebo. In Trial 2, 255 patients were randomized to etelcalcetide, and 260 were randomized to receive placebo.

Based on the findings of these two trials, etelcalcetide demonstrated a favorable effect compared with placebo on achieving a statistically significant reduction in PTH of greater than 30% in less than six weeks along with a reduction in markers of bone function. Etelcalcetide use was generally safe and well tolerated.

The results of this study concluded that etelcalcetide was noninferior and superior to cinacalcet in achieving the primary endpoint[7].

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of hyperparathyroidism treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for etelcalcetide.**

Table 9. Etelcalcetide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Etelcalcetide	NICE[8]	06/2017: Etelcalcetide is recommended as an option for treating secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis, only if: • treatment with a calcimimetic is indicated but cinacalcet is not suitable and • the company provides etelcalcetide with the discount agreed in the patient access scheme.
	CADTH	N/A
	HAS[9]	04/2017: No clinical benefit demonstrated in the treatment of secondary hyperparathyroidism in adult patients on haemodialysis compared to MIMPARA (Cinacalcet).
	IQWIG[10]	08/2017: An added benefit of etelcalcetide in comparison to cinacalcet is not proven because the company did not present any suitable data.
	PBAC	N/A

Conclusion Statement – Etelcalcetide

Etelcalcetide offers an additional choice for managing high parathyroid hormone levels in the treatment of mineral and bone disorder (MBD) associated with chronic kidney disease (CKD) in individuals undergoing maintenance hemodialysis due to end-stage renal disease (ESRD). It could be seen as an alternative treatment option when the use of a calcimimetic is recommended, but cinacalcet is not suitable or cost-effective.

It is important to note that there is conflicting data or recommendations from HTA bodies regarding the use of etelcalcetide for the management of Secondary Hyperparathyroidism in Adults with Chronic Kidney Disease on Hemodialysis. IQWIG and HAS concluded that there is no added benefit for the use of etelcalcetide in comparison to cinacalcet whereas NICE recommends the implementation of etelcalcetide in certain circumstances. Therefore, Etelcalcetide is recommended to be added to CHI formulary.

2.1.2 Denosumab

This section includes pertinent information regarding the use of denosumab (Prolia®, XGEVA®) in hyperparathyroidism:

Table 10. Drug Therapy with Denosumab

SCIENTIFIC NAME **Denosumab**	
SFDA Classification	Prescription
SFDA Approval	Yes but not for this indication
US FDA	Yes but not for this indication
EMA	Yes but not for this indication
MHRA	Yes but not for this indication
PMDA	Yes but not for this indication
Indication (ICD-10)	E21
Drug Class	Bone-Modifying Agent; Monoclonal Antibody
Drug Sub-class	N/A
ATC Code	M05BX04
Pharmacological Class (ASHP)	92:24 - Bone Resorption Inhibitors
DRUG INFORMATION	
Dosage Form	Solution for injection, Solution for injection in pre-filled syringe

Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	Primary Hyperparathyroidism • 60 mg denosumab subcutaneously every 6 months
Maximum Daily Dose Adults*	60 mg denosumab subcutaneously every 6 months
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	<u>Altered kidney function:</u> • CrCl ≥30 mL/minute: No dosage adjustment necessary. • CrCl <30 mL/minute: Prolia: No dosage adjustment necessary Xgeva: There are no specific dosage adjustments recommended. Guidelines suggest dosage adjustment is not necessary. • Hemodialysis, intermittent (thrice weekly): Unlikely to be removed by hemodialysis ; dose as for patients with CrCl <30 mL/minute; use with caution and monitor calcium levels closely, with appropriate adjustment in dialysate calcium concentration in addition to adequate calcium and active vitamin D supplementation. • Peritoneal dialysis: Unlikely to be removed by peritoneal dialysis ; dose as for patients with CrCl <30 mL/minute; use with caution and monitor calcium levels closely. <u>Hepatic Impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	ST

AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Denosumab is typically used when other treatment approaches have failed.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Peripheral edema, dermatitis, hypocalcemia, hypophosphatemia, diarrhea, nausea, anemia, thrombocytopenia, fatigue, headache, arthralgia, asthenia, back pain, limb pain, cough, dyspnea, upper respiratory tract infection. Most severe: Bone fractures, dermatologic reactions, hypersensitivity, hypercalcemia, hypocalcemia, infection, osteonecrosis of the jaw, musculoskeletal pain.
Drug Interactions	**Category X**: None
Special Population	N/A
Pregnancy	Based on the mechanism of action and data from animal reproduction studies, in utero exposure to denosumab may cause fetal harm. Denosumab is a humanized monoclonal antibody (IgG_2). Potential placental transfer of human IgG is dependent upon the IgG subclass and gestational age, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis.

Lactation	It is not known if denosumab is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Prolia: Hypersensitivity (systemic) to denosumab or any component of the formulation; preexisting hypocalcemia; pregnancy Xgeva: Known clinically significant hypersensitivity to denosumab or any component of the formulation; preexisting hypocalcemia
Monitoring Requirements	Monitor serum creatinine, serum calcium, phosphorus and magnesium (especially within the first 14 days of therapy [Prolia] or during the first weeks of therapy initiation [Xgeva]), pregnancy test (prior to treatment initiation in females of reproductive potential); signs/symptoms of hypocalcemia, especially in patients predisposed to hypocalcemia (severe renal impairment, thyroid/parathyroid surgery, malabsorption syndromes, hypoparathyroidism); signs/symptoms of hypercalcemia, including periodic serum calcium (following discontinuation in patients with giant cell tumor of the bone and patients with growing skeletons); infection, or dermatologic reactions; routine oral exam (prior to treatment); dental exam if risk factors for ONJ; signs/symptoms of hypersensitivity.
Precautions	Renal impairment: Use with caution in patients with renal impairment (CrCl <30 mL/minute) or patients on dialysis;

	risk of hypocalcemia is increased. Dose adjustment is not needed when administered at 60 mg every 6 months (Prolia); once-monthly dosing has not been evaluated in patients with renal impairment (Xgeva).
Black Box Warning	Special Alert: Risk of Severe Hypocalcemia in Patients on Dialysis Safety Alert
REMS	N/A

Clinical trials – Denosumab

"Denosumab for management of severe hypercalcemia in primary hyperparathyroidism" is the title of a retrospective study of 10 patients who received subcutaneously 60 mg of denosumab that was conducted to evaluate the effects of denosumab on calcium levels.

The tendency for calcium reduction was evident by the third day following the administration of denosumab. In most cases, a decline in serum calcium levels to an average of 2.8 mmol/L or below was typically observed by the seventh day (P = 0.002).

Denosumab's impact on RANKL signaling, its ability to hinder bone resorption driven by PTH, and its resulting decrease in serum calcium levels render it a valuable approach for managing pronounced hypercalcemia in individuals with PHPT, particularly when surgery is postponed or not feasible for certain reasons. Notably, denosumab offers advantages, including its applicability without limitations in patients with concurrent chronic kidney disease.

Health Technology Assessment (HTA)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of denosumab for the management of severe hypercalcemia in hyperparathyroidism.**

Conclusion Statement – Denosumab

Denosumab is usually used as an option for the management of severe hypercalcemia or bone resorption in hyperparathyroidism through its anti-resorptive properties as well as its ability to lead to a rapid reduction in serum calcium levels.

It is important to note that there is currently no available data or recommendations from HTA bodies specifically addressing the use of Denosumab in

hyperparathyroidism management, however, Denosumab is recommended to be added to CHI formulary.

2.2 Modifications

The strength of Calcium lactobionate, Calcium glubionate is available in the SFDA updated list, which is 0.287 g, 0.295 g.

There were no other modifications after April 2020.

2.3 Delisting

The medications below are no longer SFDA registered[11], therefore, it is advisable to **delist** the following drugs from CHI formulary. *Please refer to **Drugs in the disease - section 2** of CHI Hyperparathyroidism original clinical guidance.*

- Calcitriol

Section 3.0 Key Recommendations Synthesis

- Hypercalcemic primary hyperparathyroidism (PHPT) is defined by elevated serum calcium levels, adjusted for albumin levels, along with an elevated or inappropriately normal intact parathyroid hormone (PTH) level, as measured using a second or third-generation assay, on at least two distinct occasions, with a minimum interval of 2 weeks between each measurement[5].
- Patients diagnosed with symptomatic primary hyperparathyroidism (PHPT) and deemed appropriate candidates for surgery following an assessment of surgical risks and life expectancy should be advised to consider surgical intervention[4].
- The calcimimetic cinacalcet is expected to lower serum calcium levels without necessarily leading to improvements in bone mineral density (BMD)[5].
- For patients with symptomatic primary hyperparathyroidism (PHPT) and serum calcium levels exceeding the upper limit of normal by >0.25 mmol/L (>11.0 mg/dL), who do not undergo parathyroidectomy (PTX), we recommend considering cinacalcet (a weak recommendation based on limited evidence quality)[5].
- Regarding vitamin D supplementation, the expert panel suggests maintaining 25OHD levels above 30 ng/mL but below the upper limit of the laboratory reference range (e.g., < 50 ng/mL)[5].
- In cases of PHPT with insufficient 25OH vitamin D levels (< 30 ng/mL or 75 nmol/L) or deficiency (<12 ng/mL or <30 nmol/L), we propose considering

vitamin D supplementation (a weak recommendation based on very low-quality evidence)[5].

- Calcium intake or supplementation should align with the nutritional guidelines of the Institute of Medicine: 800 mg/day for women aged 50 and men aged >70[5].
- For individuals with low BMD who do not undergo parathyroidectomy, we recommend contemplating the use of bisphosphonates (such as alendronate) or denosumab (a weak recommendation based on very low-quality evidence)[5].
- Bisphosphonates, primarily alendronate, have demonstrated BMD improvements and reduced bone turnover in PHPT, but consistent reductions in serum calcium concentration have not been established[5].
- Women in their reproductive years who are diagnosed with primary hyperparathyroidism (PHPT) are advised to consider curative surgery before becoming pregnant, whenever possible[4].
- In the case of a pregnant woman diagnosed with severe primary hyperparathyroidism (PHPT), it is recommended to undergo parathyroidectomy during the second trimester of pregnancy. Ultrasound is the preferred approach for pinpointing the affected parathyroid gland[4].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Hyperparathyroidism report** and aims to provide recommendations to aid in the management of Hyperparathyroidism. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Hyperparathyroidism. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Hyperparathyroidism Scope

2020	Changes	2023	Rationale
Section 1.0 Hyperparathyroidism Clinical Guidelines			
Nice guidelines of Hyperparathyroidism (primary): diagnosis, assessment and initiaL management [2019]	N/A		
Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop [2014]	Updated	Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop 2022[5]	**Diagnosis** • Hypercalcemic primary hyperparathyroidism (PHPT) is characterized by an increased level of serum calcium, which is corrected for albumin levels, along with a higher or inappropriately normal level of intact parathyroid hormone (PTH) measured using a second or third-generation assay, observed on at least two separate occasions, with a minimum interval of 2 weeks between each measurement. • Familial hypocalciuric hypercalcemia (FHH) might be considered in younger individuals exhibiting a urinary calcium/creatinine clearance ratio of less than 0.01, or those who have a family history of hypercalcemia. • Lithium and thiazides are both medications that can lead to hypercalcemia and elevated PTH levels above the normal range. • The occurrence of ectopic secretion of PTH causing hypercalcemia in association

			with malignant tumors is extremely rare. • Normocalcemic primary hyperparathyroidism (PHPT) is characterized by having normal adjusted total calcium and ionized calcium levels, while showing elevated intact PTH levels (measured using a second or third generation assay) on at least two occasions spanning 3 to 6 months. This diagnosis is made after ruling out all other potential causes for secondary hyperparathyroidism. **Clinical phenotypes of PHPT** • Symptomatic PHPT: associated with overt skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis • Asymptomatic PHPT: no overt symptoms or signs; typically discovered by biochemical screening. Two forms of asymptomatic PHPT are defined after evaluation: - with target organ involvement - without target organ involvement • Normocalcemic PHPT: Skeletal or renal complications may or may not exist in those whose presentation fits this definition. **Patients Evaluation** • Biochemical: Measure adjusted total serum calcium (ionized if normocalcemic PHPT is a consideration),

			phosphorus, intact PTH, 25OHD, creatinine. • Skeletal: Three-site dual-energy X-ray absorptiometry (DXA) (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (vertebral fracture assessment [VFA] or vertebral X-rays); trabecular bone score (TBS) if available • Renal: Estimated glomerular filtration rate (eGFR) or, preferably, creatinine clearance, 24-hour urinary calcium and for biochemical risk factors for stones; imaging for nephrolithiasis/nephrocalcinosis • Nonclassical manifestations (neurocognitive, quality of life, cardiovascular): there are no data to support routine evaluation for these putative manifestations • Genetic: genetic evaluation should be considered for patients • In patients with asymptomatic PHPT, we recommend surgery to cure the disease (strong recommendation/high quality evidence). **Parathyroidectomy** • Although parathyroidectomy is an option for all patients, with concurrence of the patient and the physician and if there are no contraindications, the panel recommends surgery in all those in whom one or more of the following is present

			(including those who are asymptomatic): - Serum calcium >1 mg/dL (0.25 mmol/L) above the upper limit of normal or - Skeletal involvement: a. A fracture by VFA or vertebral X-ray or b. Bone mineral density (BMD) by T-score ≤ 2.5 at any site or - Renal involvement: a. eGFR or creatinine clearance < 60 mL/min b. Nephrocalcinosis or nephrolithiasis by X-ray, ultrasound, or other imaging modality c. Hypercalciuria (eg, >250 mg/day in women; >300 mg/day in men) or - Age < 50 years (no other indications are necessary; age < 50 years is a sufficient indication) • Surgery should be performed by an experienced parathyroid surgeon. • Surgery cannot be recommended to improve neurocognitive function, quality of life, and/or cardiovascular indices because the evidence is inconclusive. **Medical management of PHPT**

			Patients with PHPT who do not meet guidelines for parathyroidectomy can be followed without pharmacological intervention. For those who choose not to have surgery, but who meet specific guidelines (e.g., calcium or bone mineral density), medical options are available as recommended by the Panel. • The calcimimetic cinacalcet would be expected to reduce the serum calcium without necessarily improving bone mineral density (BMD). • In patients with PHPT and serum calcium levels >11.0 mg/dL (>0.25 mmol/L) above the upper limit of normal who do not undergo PTX, we suggest cinacalcet (weak recommendation based on low quality of evidence). • Vitamin D supplementation: the panel recommends levels of 25OHD >30 ng/mL and < the upper limit of normal for the laboratory reference range (eg, < 50 ng/mL) • In patients with PHPT and vitamin D insufficiency (25OH vitamin D < 30 ng/mL (75 nmol/L) or deficiency (<12 ng/mL; <30 nmol/L) we suggest vitamin D supplementation (weak recommendation based on very low-quality evidence) • Calcium intake/supplementation should follow the Institute of Medicine nutritional guidelines: 800 mg/ day for women 50 and men >70 years old. • In patients with low BMD who do not undergo PTX, we

			suggest bisphosphonates (eg, alendronate) or denosumab (weak recommendation based on very low-quality evidence) • Bisphosphonates, primarily alendronate, have been shown to improve BMD and to reduce bone turnover in PHPT, but without any consistent reductions in the serum calcium concentration. • Estrogen has been shown to increase BMD. Its effect on the reduction of serum calcium is inconsistent. • Raloxifene cannot be recommended because the data are insufficient to reach any conclusions. **Monitoring requirements in patients who do not undergo Parathyroidectomy (PTX)** • Serum calcium and 25OHD concentrations: annually. PTH levels can also be measured, as clinically indicated. **Skeletal:** • Three-site DXA every 1 or 2 years unless the BMD is normal. • Vertebral X-ray, VFA, or TBS if clinically indicated. **Renal:** • Creatinine clearance (preferred over eGFR), annually. • Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated • 24-Hour urine for calcium, if clinically indicated.

			Pregnancy considerations • Mild cases should be managed by maintaining good hydration and monitoring calcium levels. • Bisphosphonates and denosumab should not be used. • Data are very limited on use of cinacalcet. • Consider surgery in the second trimester for patients with serum calcium >11.0 mg/dL and for whom surgery is not contraindicated. • Preoperative imaging should be limited to ultrasound. • If surgery is deferred, the neonate should be closely monitored for hypocalcemia. • If surgery is deferred, PTX should be done after delivery, and before a subsequent pregnancy.
The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism [2016]	N/A		
European Society of Nephrology guidelines for Secondary Hyperparathyroidism : Pathogenesis, Disease Progression, and Therapeutic Options [2011]	N/A		

[2018] Endocrine Society guidelines of Primary Hyperparathyroidism	N/A		
	Missing	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 (2021)[4]	PHPT can be classified according to the following types: • **Classical PHPT:** Classical PHPT is characterized by high serum calcium and elevated serum PTH due to parathyroid neoplasia. Surgical removal of the affected tissue corrects hypercalcemia and improves symptoms. Up to 25% of PHPT cases may have elevated calcium with normal PTH levels. • **Normocalcaemic HPT (NCHPT):** Normocalcemic hyperparathyroidism (NCHPT) is characterized by consistently normal levels of serum PTH and both adjusted and ionized calcium within the reference range. The patient should have normal kidney function and no other secondary causes of hyperparathyroidism, such as vitamin D deficiency, kidney problems, idiopathic hypercalciuria, malabsorption, Paget's disease, or iatrogenic causes like thiazides,

			lithium, denosumab, and bisphosphonates. Limited and inconsistent data are available regarding the natural history of NCHPT, but some patients with NCHPT may eventually develop into classical hyperparathyroidism over time. • Serum calcium should be measured in patients with reduced bone mineral density, minimal trauma fractures, renal stones, in patients taking lithium, in patients with fatigue, musculoskeletal or neuropsychiatric complaints or altered mental status. • Serum calcium, PTH, and 25-hydroxy vitamin D should be measured in patients >40 years before undergoing thyroid surgery. **Diagnostic investigations and criteria** • In patients with normal kidney function and albumin levels, measure serum calcium adjusted for albumin levels. If renal function or albumin levels are not normal, use ionized calcium to assess serum calcium levels. • If a patient shows elevated calcium levels adjusted for albumin, it is advisable to repeat the test or request ionized calcium along with

			serum phosphate, renal function, parathyroid hormone (PTH), and 25-hydroxy vitamin D levels for further evaluation. • For patients with confirmed hypercalcemia, assess the urinary calcium: creatinine clearance ratio using either a 24-hour urinary calcium collection or a second morning void urinary calcium sample. This differentiation is crucial to distinguish between hyperparathyroidism and familial hypercalcemic hypocalciuria (FHH). • Individuals diagnosed with primary hyperparathyroidism are advised to undergo a DXA (Dual-energy X-ray absorptiometry) scan of the hip, lumbar spine, and distal radius. • All patients with primary hyperparathyroidism (PHPT) should undergo thoracolumbar imaging initially. Parathyroidectomy should be taken into consideration for patients with vertebral compression fractures, whether they are symptomatic or asymptomatic. • For patients with primary hyperparathyroidism (PHPT) who do not have other indications for parathyroidectomy, it is recommended to consider renal tract imaging. Possible imaging modalities include renal tract ultrasound and X-ray KUB (Kidneys, Ureters, and Bladder). A non-contrast CT scan (CT-KUB) is also a viable option, which exposes the

			patient to relatively low radiation and provides excellent sensitivity in detecting potential issues. • Even if there is no prior history of urinary tract calculi or any findings on imaging, it is still recommended to evaluate urinary calcium excretion. For patients with confirmed hyperparathyroidism and hypercalciuria, the possibility of undergoing parathyroidectomy should be considered. **Surgery** • Patients diagnosed with symptomatic primary hyperparathyroidism (PHPT) and who are considered suitable candidates for surgery based on an evaluation of surgical risks and life expectancy should be recommended for surgical treatment. • In patients with primary hyperparathyroidism (PHPT) who have an elevated risk of fractures, parathyroidectomy is recommended, considering their current bone density and fracture history. • Patients diagnosed with primary hyperparathyroidism (PHPT) and showing signs of renal tract calcification, such as nephrolithiasis (kidney stones) and nephrocalcinosis, should undergo parathyroidectomy. • For patients experiencing musculoskeletal symptoms associated with primary hyperparathyroidism (PHPT), parathyroidectomy should be

			taken into consideration as a possible treatment option. • For patients with neurocognitive and/or neuropsychiatric symptoms related to primary hyperparathyroidism (PHPT), it is advisable to consider parathyroidectomy as a recommended course of action. • Patients with slightly elevated calcium levels should undergo assessment and management similar to those with more severe hypercalcemia. **Management of asymptomatic hyperparathyroidism** • Before deciding on observation rather than surgery, asymptomatic patients with primary hyperparathyroidism (PHPT) should be evaluated for any signs of end-organ complications, such as decreased bone mineral density, vertebral compression fractures, or kidney stones. The presence of these complications would be an indication for surgery in patients with a reasonable life expectancy. • Patients diagnosed with asymptomatic primary hyperparathyroidism (PHPT) and no signs of end-organ damage, who are medically capable of tolerating anesthesia, and have a life expectancy of more than 10 years, should be provided with information regarding the advantages and disadvantages of surgical

			intervention compared to observation. • Patients who are monitored or managed medically should undergo annual evaluation. **Management of hyperparathyroidism in pregnancy** • For women of childbearing age diagnosed with primary hyperparathyroidism (PHPT), curative surgery is recommended before pregnancy, whenever feasible. • If a pregnant woman is diagnosed with severe primary hyperparathyroidism (PHPT), it is advised to undergo parathyroidectomy during the second trimester of pregnancy. Ultrasound is the preferred method for localizing the affected parathyroid gland. • In a patient with PHPT, a palpable neck mass, severely elevated calcium or PTH, and large tumor size are features suspicious for parathyroid carcinoma and should prompt careful evaluation. • Patients with primary hyperparathyroidism (PHPT) who have early onset or involvement of multiple glands, parathyroid carcinoma, a family history of PHPT or related tumors, and/or a personal history of other features associated with PHPT predisposition syndromes are recommended to undergo genetic testing. Additionally, genetic testing should be considered for

			hypercalcemic patients who exhibit features indicative of familial hypocalciuric hypercalcemia (FHH). • The choice of genes to be examined in genetic testing should be based on the specific indication for testing. In cases where a predisposition syndrome for primary hyperparathyroidism (PHPT) is suspected, the following genes should be assessed: MEN1, CDC73, RET, CDKN1B, GCM2, and CASR. On the other hand, suspected familial hypocalciuric hypercalcemia (FHH) should involve the assessment of CASR, AP2S1, and GNA11 genes.
	New	Management of primary and renal hyperparathyroidism: guidelines from the German Association of Endocrine Surgeons (CAEK) (2021)[6]	**Primary hyperparathyroidism** **Epidemiology and diagnosis of pHPT** • The biochemical assessment for diagnosing primary hyperparathyroidism (pHPT) should involve multiple measurements of serum calcium, parathyroid hormone (PTH), creatinine, and 25-hydroxyvitamin D levels (consensus ++). • To rule out familial hypocalciuric hypercalcemia (FHH), it is recommended to conduct a 24-hour urine calcium measurement (consensus ++). **Symptoms of pHPT** • The biochemical diagnosis of primary hyperparathyroidism (pHPT) should be complemented by an

			assessment of personal and family medical history, which should encompass both typical and associated symptoms of pHPT (consensus ++). • It is possible to conduct dual-energy X-ray absorptiometry (DXA) preoperatively, which can assess various skeletal areas such as the lumbar spine, femoral head, or distal radius (high consensus +++). **Indications and outcomes of surgery for pHPT** • Surgery is the sole curative treatment for primary hyperparathyroidism (pHPT). Parathyroidectomy is recommended regardless of the patient's age. In specific cases where individuals are asymptomatic with mildly elevated serum calcium levels, surveillance of pHPT can be considered (consensus ++). • Parathyroidectomy during pregnancy can be safely performed in the second trimester (consensus ++). • Parathyroidectomy is strongly indicated for patients with nephrolithiasis or nephrocalcinosis (high consensus +++) • Parathyroidectomy is recommended for individuals with osteoporosis and fragility fractures, particularly those affecting the spine or occurring after minor trauma (consensus ++). • Parathyroidectomy is recommended for patients with typical psychiatric and neurocognitive symptoms (consensus ++)

			Preoperative management of pHPT • Individuals with 25(OH) vitamin D levels below 20 ng/mL are advised to initiate vitamin D supplementation. It is also recommended to conduct short-term serum calcium testing in these patients (high consensus +++). **Hypercalcemic crisis** • Patients experiencing a hypercalcemic crisis should receive in-hospital care, which includes fluid resuscitation, followed by parathyroidectomy. • Both pre-operative and post-operative laryngoscopy should be conducted for every patient undergoing surgery for primary hyperparathyroidism (pHPT) or recurrent hyperparathyroidism (rHPT). **Operative therapy for pHPT** **Perioperative management** **4. Perioperative management** • After undergoing parathyroidectomy, there is generally no need for postoperative thromboembolic prophylaxis. However, exceptions to this are protracted and oncologic cervical procedures or situations where patients have elevated individual risk factors. (high consensus +++) • The routine use of antimicrobial prophylaxis is not generally recommended for parathyroid surgery. The

			decision to administer antimicrobial prophylaxis should be based on individual and intraoperative risk factors. (high consensus +++). **5. Intraoperative PTH monitoring** • IOPTH (Intraoperative parathyroid hormone) should be employed for focused parathyroid surgery and can also be utilized for bilateral neck exploration to rule out multiglandular disease (consensus ++). • To ensure consistency and accuracy, it is highly recommended to implement a standardized protocol for IOPTH with clearly defined interpretation criteria (high consensus +++). • The interpretation of IOPTH results should take into account intraoperative PTH peaks, delayed declines potentially caused by impaired renal function, as well as very high or low initial values (high consensus +++). • In specific, highly selective cases where there is concordant localization of a single-gland adenoma, surgeons have the discretion to decide not to use IOPTH (high consensus +++). • For defining the side of the hyperfunctional parathyroid gland, intraoperative bilateral venous sampling can be highly useful (high consensus +++). **6. Postoperative management**

			• After parathyroid surgery, patients should undergo postoperative monitoring for cervical hematoma following the guidelines typically used for thyroid surgery. In cases where secondary hemorrhage is suspected, immediate airway management and decompression are necessary. • It is highly recommended to assess postoperative parathyroid function on the first postoperative day. This assessment should include measuring calcium and PTH levels to check for hypoparathyroidism (high consensus +++). • Following a successful parathyroidectomy, around 50% of patients may experience early hypocalcemia. In approximately 10% of cases, this condition is attributed to "hungry bone syndrome." In light of this, it may be advisable to consider prophylactic supplementation with oral calcium and vitamin D (consensus ++). • In the event of postoperative hypoparathyroidism, it should be managed through the administration of oral calcium and active vitamin D. Furthermore, it is important to conduct follow-up laboratory tests to monitor and manage the condition effectively (consensus ++). **Reoperations for persistent or recurrent pHPT** • Reoperations for primary hyperparathyroidism (pHPT)

			should only be considered in patients who have positive preoperative localization studies, and these reoperations should be conducted with the use of intraoperative PTH monitoring (consensus +++). • Patients undergoing reoperative parathyroidectomy should undergo the same postoperative monitoring for cervical hemorrhage, recurrent laryngeal nerve paresis, and hypocalcemia as patients undergoing primary operations (high consensus +++). • For patients who have undergone parathyroid surgery, it is important to obtain biochemical follow-up for a minimum of 6 months. The duration of follow-up may need to be extended if hypercalcemia, hypocalcemia, or a family history of hereditary hyperparathyroidism (HPT) is identified (high consensus +++). **Renal hyperparathyroidism (rHPT)** **III. Indication for parathyroidectomy in rHPT** • In patients with recurrent hyperparathyroidism (rHPT), parathyroidectomy is recommended when all conservative treatment options have been exhausted, and clinical symptoms are present (consensus ++).

			IV. Indication for parathyroidectomy before and after renal transplantation • For symptomatic patients with recurrent hyperparathyroidism (rHPT) who are candidates for renal transplantation, subtotal parathyroidectomy may be considered as part of the treatment plan (high consensus +++). • In cases of severe symptomatic hypercalcemia occurring within the first few months after renal transplantation, a multidisciplinary medical team should be involved in the management. Early consideration of subtotal parathyroidectomy may be indicated as part of the treatment approach (consensus ++). **Preoperative localization procedures in rHPT** • For patients diagnosed with recurrent hyperparathyroidism (rHPT), it is highly recommended to undergo preoperative ultrasound. This ultrasound serves the purpose of localizing hyperplastic parathyroid glands and assessing for any concurrent thyroid disease (consensus ++) • Patients who are on dialysis face an elevated perioperative risk, and their cardiovascular comorbidities should be taken into account. In cases where patients are on dialysis, parathyroidectomy is typically

			recommended to be performed the day following the last dialysis session (high consensus +++). **Surgery for rHPT** • In the context of recurrent hyperparathyroidism (rHPT), IOPTH (Intraoperative parathyroid hormone) can be employed as a predictive tool for determining whether the condition has been successfully treated. However, defining specific criteria for PTH decrease in rHPT can be more challenging, as it depends on the PTH assay used. Therefore, the effective use of IOPTH relies on the experience and expertise of the surgeon (consensus ++). • For older patients who do not have planned renal transplantation, a parathyroidectomy without autotransplantation and without thymectomy can be considered as an option. (high consensus +++) • Regardless of the number of parathyroid glands removed during surgery, a cervical thymectomy can be carried out to reduce the risk of persistent or recurrent recurrent hyperparathyroidism (rHPT) (high consensus +++). • For autotransplantation, the least nodular altered parathyroid tissue should be selected (high consensus +++). • Cryopreservation of parathyroid tissue can be conducted after total parathyroidectomy or during reoperative parathyroid

			surgery. However, if vascularized parathyroid tissue is intentionally left in its original location, cryopreservation can be omitted (high consensus +++). • Postoperative surveillance, as well as the adjustment and reduction of the initial calcium and vitamin D medications, is advisable, particularly when these medications are initially prescribed in substantial doses. Such postoperative management should ideally be overseen by an experienced nephrologist (consensus ++). **Complications and management in patients with rHPT** • Postoperative hemorrhage following parathyroidectomy for recurrent hyperparathyroidism (rHPT) tends to occur more frequently compared to primary hyperparathyroidism (pHPT). In the event of postoperative bleeding, it is crucial to promptly perform surgical revision, and perioperative antibiotic prophylaxis should be administered as a mandatory measure (high consensus +++). • According to the multimorbidity of patients with rHPT, perioperative single-shot antibiotics should be applied (consensus ++) **Persistence and recurrence of rHPT** • For reoperative rHPT, preoperative localization

			procedures must be performed (high consensus +++). **Secondary hyperparathyroidism without renal insufficiency** • The treatment approach for secondary hyperparathyroidism (sHPT) typically involves high doses of vitamin D and possibly calcium supplementation, along with osteoporosis treatment. In such cases, there is generally no indication for surgery **Hereditary forms of hyperparathyroidism** **3. Multiple endocrine neoplasia type 1** • For patients diagnosed with primary hyperparathyroidism (pHPT) and who are younger than 30 years old, it is recommended to undergo gene mutation analysis of potential candidate genes based on their family history. This should be carried out after genetic counseling. (consensus ++). • When a MEN1 (Multiple Endocrine Neoplasia type 1) mutation is detected, it is highly advisable, to examine and monitor specific organ manifestations corresponding to MEN1. In such cases, parathyroidectomy should be performed as soon as pHPT is diagnosed (high consensus +++). • For patients with MEN1, subtotal or total parathyroidectomy, along with thymectomy and autotransplantation, is

			indicated. To minimize the risk of permanent hypoparathyroidism, selective resection of enlarged parathyroids can be considered. Additionally, patients must be informed about the possibility of reoperation for recurrent pHPT (high consensus +++). **4. Multiple endocrine neoplasia type 2a** • For pHPT in MEN2A syndrome, selective parathyroidectomy with IOPTH is recommended for markedly diseased glands (high consensus +++). **Primary hyperparathyroidism in children and adolescents** • In individuals aged 20 years or younger who present with typical symptoms such as fatigue, weakness, lack of concentration, and nephrolithiasis, it's important to note that 95% of these patients with primary hyperparathyroidism (pHPT) exhibit these symptoms. In such cases involving children or adolescents with these symptoms, it is advisable to conduct laboratory tests to measure serum calcium and parathyroid hormone (PTH) levels (high consensus +++). • Primary hyperparathyroidism (pHPT) in children and adolescents tends to be more frequently caused by smaller and ectopic adenomas. Consequently, preoperative imaging and surgery can be challenging procedures. It is recommended that these

			procedures be carried out exclusively by experienced surgeons to ensure appropriate care and management (high consensus +++).

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Hyperparathyroidism:

The following is the result of the PubMed search conducted for hyperparathyroidism guideline search:

Query	Filters	Search Details	Results
Hyperparathyroidism[MeSH Terms]	Guideline, in the last 5 years	("hyperparathyroidism"[MeSH Terms]) AND ((y_5[Filter]) AND (guideline [Filter]))	2

The following is the result of the PubMed search conducted for primary hyperparathyroidism guideline search:

Query	Filters	Search Details	Results
(((Hyperparathyroidism, Primary[MeSH Terms]) OR (Hyperparathyroidisms, Primary[Title/Abstract])) OR (Primary Hyperparathyroidisms[Title/Abstract])) OR (Primary Hyperparathyroidism[Title/Abstract])	Guideline, in the last 5 years	("hyperparathyroidism, primary"[MeSH Terms] OR ("Hyperparathyroidism"[MeSH Terms] AND "Primary"[Title/Abstract]) OR "primary hyperparathyroidisms"[Title/Abstract] OR "primary hyperparathyroidism"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	2

The following is the result of the PubMed search conducted for secondary hyperparathyroidism guideline search:

Query	Filters	Search Details	Results
(((Hyperparathyroidism, Secondary[MeSH Terms]) OR (Secondary Hyperparathyroidism[MeSH Terms])) OR (Hyperparathyroidisms, Secondary[MeSH Terms])) OR (Secondary Hyperparathyroidisms[MeSH Terms])	Guideline, in the last 5 years	("hyperparathyroidism, secondary"[MeSH Terms] OR "hyperparathyroidism, secondary"[MeSH Terms] OR "hyperparathyroidism, secondary"[MeSH Terms] OR "hyperparathyroidism, secondary"[MeSH Terms]) AND ((y_5[Filter]) AND (guideline[Filter]))	2

Appendix D. Treatment Algorithm